Study Protocol and Statistical Analysis Plan:
Preoperative Cognitive Screening in Older Surgical Patients Utility for Predicting Morbidity,
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Study Protocol

Subject Selection: This project is designed as a prospective, single-center observational study. The cohort will consist of 250 consenting subjects ≥ 65 years of age who present to the BWH Weiner Center for Preoperative Evaluation (CPE) prior to elective lower extremity joint replacement surgery. These surgeries are selected because they are common in this age group, associated with significant morbidity, and along with dementia are considered a priority area (bone and joint conditions) by AHRQ. These ages are chosen as significant clinical data demonstrate increased cognitive impairment in community dwelling elders. Eligibility criteria include: patients ≥ 65 years of age with an ASA physical status of I-IV presenting for elective joint replacement or non-cancer spine surgery. Exclusion criteria will include planned ICU admission postoperatively, history of stroke 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. 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 (and their surrogate) may be eligible to participate in a study in the CPE involving patients over the age of 65 or between the ages of 45-60. The receptionist will then provide them with a 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. Patients with known cognitive impairment will be included in the study to determine whether this information is included in the preoperative evaluation form. They will sign their own consent if they are capable and going to sign their surgical procedure consent. In the event that the patient is not capable of signing their own consent a surrogate will be asked to provide consent with assent from the patient. In our prior studies with similar patient populations less than 1% had documented cognitive impairment. The staff member will then describe the goals and risks of the study in a quiet room in the PATC and ask the patient (and their surrogate where appropriate) if they choose to participate. 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. 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), social support (MOS Social Support Survey, a 12-item selfreport questionnaire), alcohol consumption (Alcohol Use Disorders Identification Test—Consumption [AUDIT-C], a 3-item self-report questionnaire), and health and functional status (basic and instrumental activities of daily living [ADLs and IADLs, respectively, and the WHODAS]).The World Health Organization Disability Assessment Schedule 2.0 (WHODAS) is an alternative to the SF36 to measure physical health and disability. The Brief Pain Inventory (Short-Form) will be administered to assess pain before surgery. Grip strength will be measured with a JAMAR hand dynamometer as an index of frailty. 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. 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. 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. 20mL of blood will also be obtained after surgery in the PACU and also on postoperative day 1 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 60mL. However, the additional 20mL blood sample on post-op day 1 will only be collected if the Hematocrit level is 0.30 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. The remainder of the sample will be divided into 1-ml aliquots and incubated at 37°C for 15 min with phosphatebuffered saline (PBS) (control), 100 ng/ml interleukin (IL)-6, 100 ng/ml IL10, 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. Each enrolled patient will receive a business card listing the investigators' contact information and be advised to expect a follow up telephone call prior to surgery to assess cognitive function and at 6 months and 1 year after surgery to verify data elements and reassess functional outcome. Delirium will be assessed prospectively twice per day (early afternoon, early evening) on postoperative days 1, 2, and 3 by a trained study team member using the Confusion Assessment Method [CAM]. Delirium is most common on postoperative days 1-3. For functional status, the WHODAS will be administered 6-12 months postoperatively, along with the Geriatric Depression Scale to assess mood, 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, 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.

Statistical Analysis Plan

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, Charlson Comorbidity Index, 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 from the current study will be analyzed in the grant "Circulating Extracellular Vesicles as Biomarkers of Postoperative Delirium" (grant submission number 1R21 AG061696-01). The grant has now received funding. Gregory Crosby, MD, is the PI of the above grant; no changes to the current protocol will be made for this analysis. As a secondary analysis using variables collected during the course of the open enrollment phase of the study, a machine learning algorithm will be designed, to attempt to create a meaningful predictive model of postoperative delirium detection. This secondary use of data will explore the value of machine learning in anesthesiology, and its potential in predicting postoperative delirium.