Supplementary Online Content

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Supplement 1. Study protocol and statistical analysis plan

This supplementary material has been provided by the authors to give readers additional information about their work.

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Protocol for the Electroencephalography Guidance of Anesthesia to Alleviate Geriatric Syndromes (ENGAGES) Study: a Pragmatic, Randomized Clinical Trial

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WORLD HEALTH ORGANIZATION DATA SET

Primary Registry and Trial Identifying Number	ClinicalTrials: NCT02241655
Date of Registration	September 2014
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Public Title	Protocol for the Electroencephalography Guidance of Anesthesia (ENGAGES) Study
Scientific Title	Protocol for the Electroencephalography Guidance of Anesthesia to Alleviate Geriatric Syndromes (ENGAGES)

	Study: a Pragmatic, Randomized Clinical Trial
Countries of Recruitment	United States
Health Condition(s) or Problem(s) Studied	Postoperative delirium, postoperative health-related quality of life, postoperative falls
Intervention(s)	Study arm 1: EEG-Guided Anesthesia (primary intervention) The practitioners caring for patients in the intervention group will use the raw EEG waveform as well as processed EEG indices intraoperatively to guide anesthetic administration. Specifically they will attempt to limit epochs of EEG burst suppression and try to use the information provided by the EEG to safely decrease anesthetic administration. Study arm 2: Routine Anesthetic Care (Control Group) Clinicians will not be able to view the EEG-based data. Anesthesia clinicians will use routine care to determine appropriate administration of anesthesia. Falls prevention (secondary intervention): At the time of enrollment all patients will receive information on improving the safety of their home environment and on tips to improve safety in the hospital after surgery. Patients who report that they have fallen in the six months prior to surgery may receive a home visit from an occupational therapist, who will make specific recommendations to improve the safety of the home environment.
Key Inclusion and Exclusion Criteria	Inclusion Criteria a) Adults older than 60; b) competent to provide informed consent; c) undergoing major elective surgery requiring a minimum stay of 2 days postoperatively (e.g., major open cardiac, thoracic, vascular, intra-abdominal, gynecologic, urologic, orthopedic, hepato-biliary and ear, nose and throat surgery) d) enrolled in the SATISFY-SOS study Exclusion Criteria a) Unable to provide informed consent; b) undergoing neurosurgical procedures; c) preoperative delirium; d) unable to participate adequately in delirium screening including those who are blind, deaf, illiterate or not fluent in English; e) history of intraoperative awareness f) additional surgery planned within five days of index surgery
Study Type	Interventional Allocation: randomized Intervention model: parallel assignment Blinding: anesthesia practitioner not blinded to intervention, subject blinded to intervention, primary outcome assessor blinded to intervention

	Assignment: parallel Primary purpose: prevention
Date of First Enrollment	January 2015
Target Sample Size	1232
○ **Recruitment Status**	Enrolling
Primary Outcome(s)	Outcome name: incidence of postoperative delirium Method of measurement: Delirium assessment with: Either the Confusion Assessment Method or the Confusion Assessment Method for the ICU coupled with the Inouye Delirium Chart Review Method Time points of interest: from date of randomization up to 5 days postoperatively
Key Secondary Outcomes	Outcome name: postoperative health related quality of life Method of measurement: Veteran's RAND 12-item Health Survey Time points of interest: 30 days and 1 year postoperatively Outcome name: postoperative incidence of falls Method of measurement: ProFaNE falls questions Time points of interest: 30 days and 1 year postoperatively

ORGANIZATIONAL STRUCTURE AND RESPONSIBILITIES

Principal Investigator:
Michael Avidan, MBBCh

Responsibilities include: design and conduct of the ENGAGES trial, preparation of protocol and revisions, organizing steering committee meetings, and publication of study reports.

Steering Committee:

Michael Avidan, MBBCh	Daniel Emmert, MD, PhD	Sharon K. Inouye, MD, MPH
Troy Wildes, MD	Rocco Hueneke, MD	Eva M. Schmitt, PhD
Eric Lenze, MD	Tracey Stevens, MD	Brian Torres, CRNA
Susan Stark, PhD	Thomas J. Graetz, MD	Spencer Melby, MD
Eric Jacobsohn, MBChB	Jacqueline Leung, MD	

Responsibilities include: agreement of final protocol, reviewing progress of study and if necessary, changes to the protocol, coordinating with principle investigator, and communicating with trial management committee.

Operations Committee:
Michael Avidan, MBBCh
Sherry McKinnon
Hannah Maybrier
Angela Mickle
Matthew Murphy
Ravi Upadhyayula
Ginika Apakama
George Mashour
Jacqueline Leung
Eric Jacobsohn

Responsibilities include: study planning, organization of steering committee meetings, provides annual risk report to the Human Research Protection Office at Washington University, reports SAEs (Serious Adverse Events) to Washington University IRB (Institutional Review Board), responsible for maintenance of REDCap electronic database, reporting to steering committee, ethics committee applications, data verification, recruitment, randomization, and follow-up of study participants

Data Management Committee:
Anke Winter, MD, MSc
Nan Lin, PhD

Responsibilities include: statistical design of study, data verification.

Data Adjudication Committee:
Michael Avidan, MBBCh
Eric Lenze, MD
Troy Wildes, MD
Eva Schmitt, PhD
Sharon K. Inouye, MD, MPH
Guoquan Xu, MD, PhD

Responsibilities include: regularly reviewing delirium assessments, contacting trial management committee, retraining researchers if necessary.

Data and Safety Monitoring Committee:
Heather Gwynn Allore, M.S., PhD - Yale University
Donna Marie Fick, PhD, FGSA, FAAN - Pennsylvania State University
Charles W. Hogue, Jr., MD - Johns Hopkins University School of Medicine
Pratik Pandharipande, MD – Vanderbilt University Medical Center
Frederick Sieber, MD - Johns Hopkins Hospital

Safety Officer:
Charles Brown, MD- Johns Hopkins University School of Medicine

Responsibilities include: reviewing and evaluating the study data to ensure participant safety, study conduct, progress, and efficacy, and making recommendations regarding the continuation, modification, and termination of the trial.

INTRODUCTION: Postoperative delirium, arbitrarily defined as occurring within five days of surgery, affects up to 50% of patients older than sixty after a major operation. This geriatric syndrome is associated with longer intensive care unit and hospital stay, readmission, persistent cognitive deterioration, and mortality. No effective preventive methods have been identified, but preliminary evidence suggests that electroencephalography (EEG) monitoring during general anesthesia, by facilitating reduced anesthetic exposure and EEG suppression, might decrease incident postoperative delirium. This study hypothesizes that EEG-guidance of anesthetic administration prevents postoperative delirium and downstream sequelae, including falls and decreased quality of life.

METHODS AND ANALYSIS: This is a 1,232 patient, block-randomized, double-blinded, comparative effectiveness trial. Patients older than sixty, undergoing volatile agent-based general anesthesia for major surgery, are eligible. Subjects are randomized to one of two anesthetic approaches. One group receives general anesthesia with clinicians blinded to EEG monitoring. The other group receives EEG-guidance of anesthetic agent administration. The outcomes of postoperative delirium (≤5 days), falls (≤1 month) and health-related quality of life (1 month) will be compared between groups. Postoperative delirium is assessed with the Confusion Assessment Method, falls with ProFaNE consensus questions, and quality of life with the Veteran's RAND 12-item Health Survey. The intention-to-treat principle will be followed for all analyses. Differences

between groups will be will be presented with 95% confidence intervals, and will be considered statistically significant at a two-sided $p<0.05$.

ETHICS AND DISSEMINATION: ENGAGES is approved by the ethics board at Washington University. Recruitment began in January 2015. Dissemination plans include presentations at scientific conferences, scientific publications, internet-based educational materials, and mass media.

REGISTRATION DETAILS: ENGAGES is registered on clinicaltrials.gov, NCT02241655 (updated February 2015).

Strengths

- The ENGAGES study is a pragmatic clinical trial, conducted in a real world clinical setting.
- The study will enroll older patients, who are under-studied in clinical research.
- The primary outcome, postoperative delirium, is important to patients, healthcare providers and society.
- The electroencephalography-guided anesthetic protocol is straightforward and inexpensive; it would be feasible to disseminate and implement broadly.
- The study utilizes reliable and granular data from the perioperative electronic medical record and incorporates data from a large registry of postoperative patient reported outcomes.

Limitations

- A single clinical trial should seldom be regarded as definitive; if the results of this trial do suggest that EEG-guidance of anesthesia decreases postoperative delirium, it will be necessary to replicate this finding in future studies.
- While patients and those assessing the primary outcome are blinded, the inability to blind clinicians to the trial allocation group is a potential source of bias and confounding.
- The effectiveness of the electroencephalography-guided anesthetic protocol will depend on clinicians' adherence to the protocol.
- As delirium is a fluctuating disorder, it may occasionally be missed despite rigorous and validated assessment methods.
- Some patients might be unable to speak in the early postoperative period (e.g. have a tracheal tube in place), which will curtail the sensitivity of delirium assessment.

Background

Within the next forty years, >110 million Americans will exceed the age of 60,[1] and many of them (>40%) will require elective surgery.[2] The geriatric syndrome of postoperative delirium is one of the most common complications observed with the physiological stress of major surgery and anesthesia. It affects up to 70% of surgical patients older than 60, with most studies showing an incidence of 30% to 50%.[3] Delirium is an acute and fluctuating neurologic disorder that reflects a change from baseline cognition and is characterized by the cardinal features of inattention and disorganized thinking.[4] Postoperative delirium typically first manifests between 24 and 96 hours following the surgical intervention. While it is unclear why postoperative delirium occurs so frequently, consistently described risk factors for delirium include older age, male sex, mild cognitive impairment, dementia, sensory impairment, and chronic medical illness.[5]

Postoperative delirium has substantial implications at a societal level, for healthcare professionals and for individual patients and their families. It is estimated that delirium is associated with additional healthcare costs exceeding $60,000 per patient per year.[6] Both the occurrence and the duration of delirium are linked with increased morbidity and mortality, prolonged length of hospital and intensive care unit (ICU) stay, as well as functional and cognitive decline necessitating nursing home or long-term care facility placement.[7-10] Preoperative surveys completed by 1,000 patients at our institution, Barnes-Jewish Hospital, a tertiary care facility at Washington University in St. Louis, showed that approximately 40% of surgical patients highlight postoperative delirium (or acute confusion) as one of their top concerns, and 30% of all patients are worried that they will still have problems thinking normally when they return home to recover. Another survey study showed that, when in-hospital delirium occurs, patients' family members are deeply affected by both the acute neurologic deterioration and the impact upon recovery.[11]

Delirious patients are unable to participate effectively in rehabilitation and are therefore susceptible to other postoperative geriatric syndromes and adverse events, including falls, pressure ulcers, functional decline, pneumonia, hospital readmission, and discharge to a nursing home or extended care facility.[8,12-16] There is even evidence that patients who have periods of delirium while in hospital may continue to experience persistent delirium after going home and among these patients, the risks of mortality, institutionalization, and functional and cognitive decline are even worse than those patients who experienced delirium but recovered.[17] Patients who experience postoperative delirium report persistently decreased quality of life.[8] Furthermore, additional studies suggest that incidence and duration of delirium may be associated with long-term postoperative cognitive dysfunction.[18,19] It is therefore a public health priority to test plausible interventions to prevent, identify and treat postoperative delirium.

Even though postoperative delirium is a pressing healthcare concern, there are barriers to making progress in its prevention and treatment. Delirium is difficult to diagnose as most patients with delirium are hypoactive or lethargic,[20] while medical staff typically recognize delirium when patients are hyperactive and agitated. Hypoactive characteristics may also be easily regarded as a normal phenotype in a patient recovering from surgery or general anesthesia. Furthermore, no group of healthcare practitioners involved in the direct surgical care of patients has taken ownership of delirium as a priority needing their attention. It is not currently standard of care to routinely assess surgical patients for delirium, approaches for preventing postoperative delirium have not been applied to surgical patients, and treatment options for delirium are limited. Delirium is a common complication of surgery and anesthesia with serious consequences for patients and their families, yet it remains an orphan problem and no effective prophylactic or curative treatments for postoperative delirium have been identified.

Detecting delirium routinely in surgical patients using a validated and practical approach like the Confusion Assessment Method (CAM),[21] could allow target therapies and potentially improve outcomes. For example, the Hospital Elder Life Program (HELP)[22,23] has been demonstrated to be effective for prevention of postoperative delirium, and principles and protocols from this program will be utilized in the proposed study. In addition, although the effectiveness of the Acute Care for Elders model has not yet been evaluated in the postoperative setting, delirious patients could be targeted to receive components of this model (frequent medical review,

early rehabilitation, early discharge planning, prepared environment, patient-centered care), all of which have been shown to decrease geriatric syndromes, such as falls, in vulnerable patients.[24,25] Identifying and if possible preventing delirium in surgical patients might present an important opportunity to improve numerous outcomes beyond a reduction in the delirium burden.

Although it is very likely that anesthetic management contributes to the occurrence of postoperative delirium, to date there are no validated anesthetic approaches to preventing delirium. Four randomized, controlled studies in diverse surgical settings have suggested a decrease in postoperative delirium with bispectral index (BIS) guidance of general anesthesia.[26-29] The BIS is one of several proprietary electroencephalogram (EEG) indices of anesthetic depth, based on EEG waveform processing, with numbers approaching 100 suggesting arousal or wakefulness, and numbers approaching 0 reflecting absent detectable brain electrical activity.[30] A meta-analysis of these four randomized controlled trials showed that EEG (or BIS) guidance of anesthesia was associated with a marked reduction in postoperative delirium with a pooled odds ratio of 0.56 (95% CI, 0.42–0.73, heterogeneity P value = 0.54).[29] Also of interest are several studies that have examined the relationship between low intraoperative BIS values and intermediate term postoperative mortality.[31-35] Building on these a study has demonstrated that intraoperative EEG burst suppression specifically, especially when coinciding with hypotension, is associated with increased 90-day postoperative mortality.[36]

Figure 1: Stylized common electroencephalograph (EEG) patterns from frontal EEG channel seen with progressively increasing anesthetic depth. BIS, bispectral index

Despite the findings from these studies and recommendations from the National Institute for Health and Care Excellence in the United Kingdom that electroencephalography guidance of anesthesia should be routine for vulnerable patients,[37] intraoperative EEG monitoring has not become standard anesthetic practice, and there is ongoing controversy about the utility of electroencephalography guidance of anesthesia.[38] For example, in the United Kingdom only 2% of anesthesia practitioners routinely incorporate EEG monitoring in their practice,[39] and it is possible that adoption is similarly low in the United States. The results of several clinical trials have led anesthesia practitioners to question whether EEG-guidance meaningfully changes anesthetic administration in real world settings,[40-42] and the mechanisms by which EEG-guidance could decrease postoperative delirium have not been clarified. In the United States, the American Society of Anesthesiologists in its most recent guidelines on brain monitoring does not recommend EEG monitoring as standard care for any patient population, procedure or anesthetic technique.[43] A pragmatic, randomized clinical trial would address this controversy and could help to inform the standard of care going forward. The plausibility for EEG-guidance preventing postoperative delirium is that it might help practitioners to avoid excessive anesthetic administration to vulnerable patients.[44] During general anesthesia, BIS values <30 are usually reflective of periods of EEG burst suppression,[45,46] which is often indicative of excessively deep anesthesia (See Figure 1). One study found a specific association between low BIS values and postoperative delirium, and the investigators hypothesized that burst suppression could be linked to postoperative delirium.[28] An observational study in cardiac surgery patients reported an association between intraoperative burst suppression and postoperative delirium[47], and similarly EEG suppression in critically ill patients reportedly predicts post-coma delirium.[48] Both EEG burst suppression and low BIS values have sometimes been shown to be associated with intermediate term mortality after surgery and critical illness.[31-36,49,50] The proposed Electroencephalography Guidance of Anesthesia to Alleviate Geriatric Syndromes (ENGAGES) study is designed as a parallel group, pragmatic, superiority trial to test whether a simple EEG-guided protocol, designed to minimize epochs of low BIS values and EEG burst suppression, prevents postoperative delirium as well as its downstream public health sequelae, such as deterioration in health-related quality of life and injurious falls. The ENGAGES study has three main hypotheses: 1) EEG-guidance of anesthesia is effective in preventing delirium; 2) through prevention of delirium, EEG-guided anesthesia prevents postoperative falls and improves patient reported quality of life; and 3) providing a targeted safety intervention will prevent postoperative falls.

Methods

Research Design Overview (See Figure 2)

The Human Research Protection Office at Washington University School of Medicine has approved the study. This protocol, which details the design of the ENGAGES study, includes all the elements elaborated in the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist.[51,52] The ENGAGES study will be a pragmatic randomized clinical trial enrolling 1,232 patients 60 years and older who will undergo elective major surgery at Barnes Jewish Hospital, St. Louis, MO. This hospital is an academic medical center in the Midwestern United States, which is affiliated to Washington University School of Medicine and serves a diverse range of patients in St. Louis and its environs. Eligible patients will often be recruited through the Center for Preoperative Assessment and Planning (CPAP) clinic at Barnes Jewish Hospital. Surgical patients might also be enrolled on hospital wards prior to their surgery. Participants will be randomly assigned to receive the electroencephalography-guided protocol or routine care. Assessments will be conducted at baseline, in the postoperative period during the hospital stay, at 30 days and at 1-year post-surgery. The primary outcome measure will be the incidence of postoperative delirium. During the 1-year follow-up period, health-related quality of life information and information on incident falls will be collected. At Washington University, surgical patients have been enrolled in the **S**ystematic **A**ssessment and **T**argeted **I**mprovement of **S**ervices **F**ollowing **Y**early **S**urgical **O**utcomes **S**urveys (SATISFY-SOS - NCT02032030) study since 2012. For the exploratory aim 3, there will be a prospective comorbidity-matched cohort study using the ENGAGES clinical trial population and reference subjects from the ongoing SATISFY-SOS study. There is ongoing rolling enrollment of participants to the SATISFY-SOS study, and information on patients is continuously being collected, updated and stored in a SQL Server database (Microsoft®, Redmond, WA) hosted by the Institute of Quality Improvement, Research and Informatics at Washington University.

Figure 2: Flow diagram showing design overview for ENGAGES study

Study Subjects

This study proposes to enroll 1,232 patients who are already enrolled in the SATISFY-SOS study. Patients 60 years old and older, who are competent to provide informed consent and who are undergoing major elective surgery under general anesthesia with a potent volatile anesthetic agent that requires a minimum stay of 2 days postoperatively (e.g., open cardiac surgery, open thoracic surgery, major vascular surgery, intra-abdominal surgery, open gynecologic surgery, open urologic surgery, major orthopedic surgery, open hepato-biliary surgery and major ear, nose and throat surgery) will be eligible for inclusion. As there are no absolute contraindications to EEG monitoring, the ENGAGES study is designed as a practical trial that will have minimal exclusions and therefore maximum applicability. Neurosurgical procedures will be excluded as surgery on the brain can confound the outcome (postoperative delirium). We will also exclude patients with preoperative delirium and patients who are unable to participate adequately in delirium screening including those who are blind, deaf, or illiterate or not fluent in English. Patients with a history of intraoperative awareness during intended general anesthesia will also be excluded.[53] Patients will be excluded if, prior to their index surgery, a second surgery is planned to occur within five days after the index surgery. Figure 3 outlines the flow of participants in the ENGAGES study.

Figure 3: Flow of participants

Recruitment

All consented patients will provide written informed consent for the study. Subjects will often be recruited through the CPAP clinic at Barnes Jewish Hospital, St. Louis, MO. The majority of adults undergoing surgery at Barnes-Jewish Hospital, about 30,000 patients per year, are evaluated at CPAP. This clinic is staffed by anesthesiologists specializing in perioperative medicine and nurses who aim to evaluate each surgical patient's perioperative risks. On average, the time frame between study enrollment at the CPAP clinic and elective surgery will be one week. Surgical patients might also be enrolled on hospital wards prior to their surgery.

After the research team has established the reliability of the delirium assessments, 100 patients will be enrolled

to the pilot phase of the ENGAGES trial during the first year. In years 2-4 an accrual rate of 300 to 400 patients per year is anticipated. To maximize efficiency, data from the pilot will be included in the main study.[54] In this pilot cohort, practical aspects of the trial's conduct will be evaluated. These include the feasibility of enrolling adequate numbers of patients in the preoperative assessment clinic; the ability of researchers to conduct the baseline preoperative assessments; the demonstration of retrieval of complete perioperative data (including repeated measures of EEG-derived parameters) from the electronic medical record; successful daily postoperative delirium assessments until postoperative day 5 or hospital discharge; for patients that remain delirious at day 5 they will be assessed until they return to baseline or until postoperative day 10, and near complete (>80%) 30-day patient reported outcomes data.

Based on data from previous large clinical trials completed at our site, we expect the study population to be largely gender-balanced and representative of our environs. In two of our previous studies, we enrolled 6,700 patients in St. Louis, Missouri. Results showed slightly higher enrollment of males versus females (55% vs. 45%), and racial demographics of approximately 80% white and 20% black or other.[40,41] These results are generally representative of the population in metropolitan St. Louis and surrounding regions where the majority of our patients reside. Based on 2011 census data, median household income and education levels of the population of St. Louis metropolis are representative of the national average. The ENGAGES Study will enroll patients older than 60. Older patients constitute a vulnerable population and have often been under-represented in clinical research. We anticipate that the patients enrolled in the ENGAGES Study will be broadly representative of the older adult population of the United States, recognizing that certain demographics (e.g. Hispanic) are under-represented in St. Louis. The follow-up period after randomization is approximately 1 year.

Randomization and Blinding

Randomization will be performed at the patient level using computer-generated assignment. Eligible patients who provided written informed consent will be randomized to receive the intraoperative electroencephalography-guided protocol or routine care. In order to ensure that there is not major imbalance between group assignments with respect to history of falls and cardiac surgery, subjects will be randomized (1:1) between the EEG-guided and routine care groups in blocks of 20 within these four strata (i.e., cardiac surgery with a history of falls within 6 months, cardiac surgery without a history of falls within 6 months, non-cardiac surgery with a history of falls within 6 months; and non-cardiac surgery without a history of falls within 6 months). Trained members of the research team will enroll participants and will implement the assignment of participants to the EEG-guided or usual care protocols. Group assignment will be revealed to members of the anesthetic team only when the patient enters the operating room by opening a sequentially numbered, opaque, sealed envelope in a sequence generated by one of the study's data analysts. Patients and their families will be blinded to group allocation and different members of the research team will assist with the intervention in the operating room (will not be blinded to the intervention) from those conducting the postoperative assessments (will be blinded to the intervention).[51,52] To reduce predictability of a random sequence, details of patients already randomized and prior group assignments will be recorded in a separate document that is unavailable to those who enroll participants and assign interventions.

Primary Intervention – EEG-guided Anesthetic Protocol

The primary intervention to which patients will be randomized in this study is a pragmatic EEG-guided anesthetic protocol (See Appendix). All anesthesia practitioners will receive a targeted educational session on recognition of EEG patterns typically occurring during general anesthesia. The content will be similar to that described in an article where we demonstrated that anesthesiologists could estimate BIS (processed EEG index) values fairly accurately based on clinical context and examination of the raw EEG waveform.[55] The Bispectral Index proprietary processed EEG monitor will be used for the ENGAGES study. However, the anesthesia monitor in the operating room will be configured to display, in addition to the processed EEG index, the raw EEG waveform as well as non-proprietary EEG-derived numerical values, including the burst suppression ratio and the spectral edge frequency. (Figure 4) The hypothesis motivating this study is that avoidance of EEG burst suppression during anesthesia can prevent postoperative delirium (Aim 1 in Figure 2) and its downstream consequences (Aim 2 in Figure 2). Therefore, practitioners will specifically be instructed to regularly inspect the EEG waveform for evidence of burst suppression, which is easily recognized (See Figure

1). The occurrence of burst suppression is the chief trigger for decreasing anesthetic administration in this protocol. An audible low-BIS alarm will be set at a threshold of 40, as there is an increased likelihood of epochs of EEG burst suppression below this value.[45] BIS values less than 40 will be a secondary trigger for decreasing anesthetic administration. Importantly, the EEG-guided protocol is suggestive rather than prescriptive. Clinicians should exercise judgment and might intentionally deviate from the protocol depending on the clinical situation. In both groups there will be an audible alarm for low volatile anesthetic agent (at 0.3 minimum alveolar concentration or at the clinician's discretion), which is standard practice at our institution to prevent intraoperative awareness. BIS EEG sensors will also be applied to patients in the control group for the purpose of data comparisons between groups, but when a patient is assigned to the control arm, practitioners will be blinded to all the EEG and BIS parameters, and will only see the signal quality index (SQI) of the EEG montage (Figure 5). EEG monitoring may continue to be acquired via continuous recordings of EEG, eye movements, and chin muscle activity for patients that are admitted to the ICU and step-down wards, or if the hospital room allows. Patients and research assistants assessing the study outcome measures (e.g., delirium assessments) will be blinded to the allocated intervention.

Figure 4: The anesthesia monitor is configured for the EEG-guided arm such that the raw electroencephalograph (EEG) waveform as well as the non-proprietary numerical values are displayed by the monitor, including the burst suppression ratio (SR) and the spectral edge frequency (SEF). The EEG filter is turned off so the low frequency slow delta waves (with a frequency of about 0.5 Hz.) are clearly visible. Turning off the filter allows EEG waves <2 Hz to be seen. The filter is a bandpass filter from 2 Hz to 70 Hz with a notch to eliminate 60 Hz alternating current electrical noise. With the filter off, the system has a bandwidth of approximately 0.25 Hz to 100 Hz.

Figure 5: The anesthesia monitor is configured for the control arm such all the EEG and BIS parameters are hidden, and only the signal quality index (SQI) of the EEG montage is visible.

Ensure practitioner fidelity to the EEG-guided protocol

In order for any monitor to alter clinical practice, clinicians must be able to glean useful information from the monitor and should be motivated to make decisions based on that information. One of the limitations regarding EEG guidance of anesthesia is that teaching on electroencephalography is currently limited in both anesthesiology residencies and in nurse anesthesia training programs. Given this, it is unsurprising that EEG-based monitors have not been incorporated into routine anesthetic practice. Our research group published a study showing that with a focused training session, anesthesiologists could learn to appreciate some of the key EEG changes that occur with general anesthesia.[55] We demonstrated that clinicians could learn relatively rapidly to integrate clinical context with EEG waveform information and could even accurately estimate BIS values – an index derived via computer-based processing of the raw EEG signal.[55] With initiation of the ENGAGES study, we launched a training module on a non-profit international educational website, **I**nternational **C**onsortium for **E**lectroencephalograph **T**raining of **A**nesthesia **P**ractitioners (www.icetap.org), titled "EEG Waveforms and Depth of Anesthesia".[56] Key to the success of the ENGAGES study will be educating anesthesia practitioners at our institution about the EEG waveform and how information from the EEG can be useful in guiding anesthetic practice. Regarding EEG-derived parameters specifically, we capture electronically both proprietary (e.g., BIS values) and non-proprietary (e.g., burst suppression ratio) data. Therefore, we shall be able to ascertain from the phase 1 pilot study of 100 patients whether or not the EEG-guided protocol alters anesthetic administration (e.g., measured concentrations of volatile anesthetic agents) or EEG parameters (e.g., cumulative duration of EEG burst suppression). Given that the hypothesis of the ENGAGES study is that EEG guidance in the real world can alter anesthetic management, which in turn prevents postoperative delirium, an essential proof of concept step in the pilot phase is to demonstrate our ability to alter anesthetic practice in a range of practitioners when they utilize the EEG-guided protocol.

Secondary Intervention – Multi-Component Safety Intervention

Based on findings that multi-component non-pharmacological protocols can improve sleep, decrease episodes of delirium, and improve outcomes,[20,57,58] the ENGAGES study will implement a multi-component intervention including principles from the Hospital Elder Life Program[59,60] for all patients enrolled in the study to attempt to prevent post-discharge falls and decrements in health-related quality of life.[20,57,58,61] These outcomes will be tracked in all patients in the ENGAGES study as they will also be enrolled in the SATISFY-SOS study. Likewise, these outcomes will be ascertained in a matched cohort of controls from the SATISFY-SOS cohort who will not be enrolled in the ENGAGES study. This will allow comparison in these outcomes between patients receiving the multi-component safety intervention and matched controls (Aim 3 in Figure 2). The interventions, implemented mainly after hospital discharge, will include the following, as indicated: reduction of psychoactive drugs; advice on non-pharmacological approaches to manage sleep, anxiety, and agitation; involvement of family members in care, particularly for reorientation and prevention of self-harm; encouragement of mobility and self-care; ensuring that, if needed, patients have glasses, hearing aids, and dentures; home visits by occupational therapists; targeted home safety modifications; keeping patients involved in their care; and communicating regularly with patients and their families.[20] During the pilot phase, patients and their family members will be called and questioned about their perception of the utility of the educational resources and, if relevant, the home visit.

Preoperatively, at the time of providing informed consent for the ENGAGES study (but prior to randomization for the primary intervention), all participants and their families will receive general information on delirium and falls derived from the Hospital Elder Life Program[59,60] and from the Agency for Healthcare and Research Quality-Rand (AHRQ-Rand) hospital fall prevention program.[62] The research team will provide participants and their families with information about making the home environment safer to decrease the risk of falls and related injuries. An information sheet on improving safety in the hospital after surgery will also be provided (Appendices: See CDC Fall Safety Information Sheet and Partners HealthCare Falls T.I.P.S.:Tips to Avoid Falls While in the Hospital). Postoperatively, prior to hospital discharge, the research staff will review participants' current medications and provide recommendations regarding any medications with the potential to increase the risk of falls.[63-69] We will provide participants' physicians with information about any identified medications associated with fall or delirium risk (e.g., strong centrally-acting anticholinergics, benzodiazepines)

and recommendations.[70] Many of these targeted medications were highlighted in the recent American Geriatric Society Beers Criteria guidelines as potentially inappropriate medications for older persons.[70]

Because a history of falls in older adults is associated with increased fall risk[71] the research staff may recommend and provide (if acceptable to patients and if patients live <45 miles from the hospital) home occupational therapy visits that have the general aim of improving daily activity performance/safety and prevention of falls. Because delirium in older adults is associated with increased fall risk[72-76] the research staff will recommend that patients' families exercise increased vigilance when delirium features are noted in the hospital or after hospital discharge. Patients and their families will also be reminded about the home safety assessment tool that they received at the time of enrollment (Appendix: See CDC Fall Safety Information Sheet).

Data Collection

Baseline assessment will take place at the CPAP clinic and include demographic information, a detailed medical history, physical examination, assessment of preoperative quality of life, and evaluation of falls history. Delirium will be assessed daily in the postoperative period of the hospital stay. Data collected specifically for the ENGAGES study, such as the daily delirium assessments, will be entered into the Washington University School of Medicine Research Electronic Data Capture (REDCap) application.[77] In the ENGAGES study, EEG data (including BIS values and EEG burst suppression durations) will be collected in the intervention group as well as in the blinded control group.[36,50] Furthermore, perioperative data (including repeated measures data) will be retrieved from the hospital's perioperative electronic medical record (Metavision by *i*MD*soft*®, Needham, MA).[36,41,53,78] We are able routinely to capture high fidelity perioperative data from our MetaVision to an SQL server (Microsoft, Redmond, WA) database. Routinely acquired data include detailed patient medical history, surgical history, specific patient risk factors, medications, Barthel Index, VR-12 quality of life data, Short Blessed Test, sleep apnea screening, laboratory data, intraoperative medications, physiological readings, and postoperative recovery parameters. Olfaction might be assessed preoperatively with the Brief Smell Identification Test, as hyposmia has been identified as a risk factor for postoperative delirium.[79] All the data for SATISFY-SOS are integrated from various data sources and are stored in a single data repository housed in the Department of Anesthesiology at Washington University.

Cognitive Testing

When patients are assessed for delirium, structured cognitive appraisal is performed, which gives the interviewer an opportunity to make observations that are used when scoring the CAM. In addition, as part of the routine preoperative assessment, patients will be screened for cognitive impairment with the AD-8 dementia screen[80] and with the Short Blessed Test.[81] Tests from the cognitive battery of the NIH toolbox might also be incorporated in the baseline assessment.[82,83] This computer based battery assesses Executive Function, Attention, Episodic Memory, Language, Processing Speed and Working Memory (See Appendix). Depending on time constraints, patients might complete a long form of the cognitive battery or a version focused on executive function, episodic memory and attention. Patients who prefer not to do computer based cognitive tests will be offered paper based cognitive tests (Trails A and B, and Stroop Color and Word Test). Impaired performance on preoperative cognitive tests is reportedly associated with postoperative delirium[84,85], and postoperative delirium has been found to be associated with persistent postoperative cognitive decline.[18] Therefore, when patients are followed up postoperatively at thirty days, the Short Blessed Test will be administered on the telephone. When patients are followed up postoperatively at one year, the Short Blessed Test will be administered on the telephone and, if possible, follow up cognitive assessment with the NIH toolbox will be arranged. Permission from the NIH has been obtained to use the NIH Toolbox for the ENGAGES study.

Frailty Assessment

Various components of frailty are assessed routinely in the CPAP clinic and as part of the SATISFY-SOS study. These include weight loss, Charlson Comorbidity Index, individual co-morbidities, preoperative anemia

(hematocrit <35%), functional status, 6 months history of falls and the Barthel Index.[86] In addition to these measures, for the ENGAGES study we plan to measure grip strength and the Timed Up and Go (TUG) test.[86] Grip strength will also be assessed with three measurements in the dominant hand using a Jamar® handheld dynamometer (Lafayette Instruments, Lafayette, IN).[87] Maximal grip strength will be selected for analysis.

Patients' Postoperative Health and Wellbeing

All patients enrolled in the ENGAGES study will already have provided informed consent for the SATISFY-SOS study. Using the SATISFY-SOS infrastructure, the ENGAGES study will track postoperative patient reported outcomes at approximately 1 month and at 1 year. Patient reported outcomes tracked include health-related quality of life and postoperative falls.

Outcome Measures

i) Incidence of Postoperative Delirium (Aim 1 in Figure 2)

Incident delirium is the primary outcome of the ENGAGES trial. A preoperative baseline assessment will be performed when patients are enrolled to participate in the ENGAGES study. Preoperative delirium is rare before elective surgery and will exclude participation in the study. Postoperative delirium assessments will be performed when patients can be aroused sufficiently in order to be assessed for delirium (Richmond Agitation-Sedation Scale (RASS) > -4). Patients will be assessed for delirium once daily in the afternoon / evening. Each patient will be assessed for delirium up to postoperative day 5; for patients that remain delirious at day 5 they will be assessed until they return to baseline or until postoperative day 10, postoperative delirium typically first manifests 24-96 hours after surgery. Delirium will be diagnosed based on a combined approach consisting of standardized daily Confusion Assessment Method (CAM) evaluations coupled with structured chart review. The CAM has been described as a viable tool to be used by non-psychiatrists for delirium detection.[21] It has subsequently been validated in numerous studies, and has a sensitivity of >94% and a specificity of >89% against a reference standard.[88] Trained research team members who are blinded to treatment allocation will assess patients for incident delirium (primary outcome) using the Confusion Assessment Method (CAM).[21] Patients who are unable to speak (e.g., have a tracheal tube or tracheostomy) will instead be assessed using the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) instrument.[89,90] Both of these methods (the CAM and the CAM-ICU) have been shown to be reliable and to have good agreement with the DSM-IV criteria for delirium.[90-92] In addition to the CAM or the CAM-ICU, an independent trained clinical researcher, blinded to the CAM results, will conduct structured chart reviews to detect episodes of delirium. A combined approach (CAM interview or CAM-ICU plus chart review) increases the sensitivity and retains specificity in detecting incident delirium.[93,94] Therefore, either a positive clinical delirium assessment (CAM or CAM-ICU) or a positive assessment for delirium based on a validated, structured chart review[93,94] will be diagnostic of incident delirium in the ENGAGES trial. The use of the structured chart review will both improve sensitive and contribute to the pragmatic aspects of this trial, since it will abstract incident delirium from a routinely available source. The trial staff will undergo training on the chart review methodology by a skilled chart reviewer under the supervision of Drs. Inouye and Schmitt.

The CAM assessment that will be used in the ENGAGES study was developed by Dr. Inouye and colleagues.[21] All ENGAGES CAM assessments will be performed by study team members who have undergone a rigorous training process. Several members of the research team participated in a full-day CAM training program led by Dr. Inouye, the original creator of the instrument.[95] Those who attended this initial training will oversee the training of other team members. All trainees must demonstrate competence at conducting the structured interviews and in correctly scoring subjects. Trainees must first conduct at least two satisfactory CAM assessments in subjects not enrolled in the ENGAGES study in the presence of a trained team member. To establish competency in scoring the CAM, trainees will observe CAM interviews conducted by trained team members and will score the CAM independently. The trainee must agree with the trainer on the presence or absence of all twelve cognitive features assessed by the CAM on a minimum of two delirious and two non-delirious patients. After meeting the stipulations of training, the newly trained team member will conduct their first interview of a patient enrolled into the ENGAGES trial in the presence of a previously trained team member. Independent of the training process, all ENGAGES team members who are participating in CAM

assessments must view and rate nine videos of standard interviews of actors depicting delirious and non-delirious patients. This process will help to demonstrate the success of the training process and the extent to which researchers reproducibly score the CAM. To establish the reliability of delirium assessments in the clinical setting, trained members of the research team will separately assess 30 patients not enrolled in the ENGAGES study at similar time points (e.g., within two hours of each other). These assessments will determine the test-retest reliability of delirium assessments by the research team. This approach will provide > 90% power to demonstrate a Kappa statistic of >0.6, representing substantial or greater agreement between raters.[96]

A structured process will be implemented to assess and ensure the quality of the delirium assessments. Every delirium assessment will be reviewed within three days with a fellow member of the research team to assess internal consistency of scoring and completeness. On a weekly basis, investigators at Washington University will review all the delirium assessments, will address methodological inconsistencies, and will attempt to resolve controversies. Monthly, there will be a teleconference including investigators from Hebrew SeniorLife/Harvard University and from Washington University to review challenging delirium assessments and to ensure that the rigor of assessments remains appropriate. During these conferences, the need for focused and comprehensive refresher training in delirium assessment[95] will be determined.

If participants agree, these assessments may be videotaped for training and education of the research team. The videotapes will include the patients face.

ii) Health-related Quality of Life (Aims 2 and 3 in Figure 2)

As part of the ongoing SATISFY-SOS study, patient self-reported Health-related Quality of Life information will be assessed through the Veteran's RAND 12-item Health Survey at baseline (preoperatively) and during follow-up (30-day and 1-year). The VR-12 was derived from the Veterans RAND 36 Item Health Survey (VR-36) and contains 12 items relating to quality of life, including physical and mental health, as well as specific questions about functional status. Physical and Mental Health Summary Scores will be calculated. The VR-12 has been validated and is widely applied as a metric for tracking health-related quality of life in the United States.[97]

iii) Falls (Aims 2 and 3 in Figure 2)

In the baseline (preoperative) questionnaire for the SATISFY-SOS study, patients are asked to indicate how many times they fell during the past 6 months and injuries from falls are ascertained. Patients who fell at least one time during the past six months will be classified as having a previous history of falls. On the 30-day and 1-year follow-up postoperative questionnaires, patients are asked to indicate whether they have experienced a fall. Based on this information, we will define two outcomes measures: Falls within 30-days and falls within 1-year of surgery. Data on number of falls and injurious falls will also be collected. The wording for the falls questions used in SATISFY-SOS is based on the definition proposed by the Prevention of Falls Network Europe (ProFaNE); the calculation for severity of fall is based on a standard algorithm.[98-100]

Pre-specified additional analyses and sub-studies

The primary aim of the ENGAGES study is to determine whether an EEG-guided anesthetic protocol can decrease postoperative delirium and its associated downstream negative sequelae (e.g., decrement in quality of life, falls). However, it is important that large, randomized trials collect and report data on multiple clinically relevant outcomes to maximize scientific yield and efficiency. The ENGAGES trial will have the potential to contribute new information on diagnosis of postoperative delirium, risk factors for postoperative delirium, and negative outcomes following incident postoperative delirium. The ENGAGES trial will be conducted using the infrastructure of the ongoing SATISFY-SOS study, which is systematically collecting detailed information on surgical patients' characteristics, and is tracking their health and well-being up to 5 years postoperatively. The effect of anesthetic depth on postoperative morbidity and mortality is currently being explored in the 6,500 patient Balanced Anaesthesia Trial.[101,102] Information provided by the ENGAGES study will add to the growing body of evidence regarding the hypothesized effects of anesthetic depth on surgical outcomes. Prespecified sub-studies for the ENGAGES trial are elaborated in an addendum at the end of this protocol.

Patient Centered Approach

Several aspects of the ENGAGES study are patient centered in their conception. There is a community liaison group that has been actively involved in the design and in the conduct of the study. Important outcomes in the study are based on patient reported outcomes measures. Both patients and their families are provided with educational material on delirium, its risk factors and its sequelae. The study also includes patient self-assessment for delirium and implementation of the validated Family Confusion Assessment Method (FAM-CAM)[103,104] instrument both in hospital and after hospital discharge. Both of these will be included in pre-specified sub-studies of the ENGAGES trial (see addendum).

Statistical Analyses

i) Effectiveness of EEG-guided anesthesia protocol in reducing incident postoperative delirium compared with usual anesthetic care (Aim 1 in Figure 2)

We will follow the intention-to-treat principle for all analyses. The primary endpoint of our analysis is the incidence of postoperative delirium as defined previously. The incidence of delirium will be compared between groups using a chi-square test, and the difference in delirium incidence with 95% confidence intervals will be calculated. Prespecified exploratory subgroup analyses: we will test for effect modification by known baseline delirium risk factors (i.e., age [<70 and ≥70], sex, history of falls, and type of surgery [cardiac versus non-cardiac]).

ii) Effectiveness of EEG-guided anesthesia protocol in improving patient reported outcomes of health-related quality of life and preventing postoperative falls (Aim 2 in Figure 2)

Health-related quality of life

Random effects regression models based on PROC MIXED in SAS will be used to compare Physical Summary Score change over 12 months between the intervention and usual care group by introducing terms for time, indicator variables for treatment group and time x treatment group interactions with the latter set of regression coefficients of primary interest. The model will be controlled for baseline health-related quality of life. Potential confounding factors including age, gender and relevant comorbidities will be evaluated and controlled for in the model. We will utilize the same analysis approach to evaluate the Mental Summary Scores.

The analysis is primarily based on the following model: $Y_{it} = \alpha + \beta_1 t + \beta_{2A} X_{i1} + \beta_{3A} X_{i1} t + \beta_4 t Y_{i0} + e_{it}$ (1)

where Y_{it} = QOL for subject i at time t, where t = 0 for baseline, t = 1 for 12 months. X_{i1} = 1 if ith subject is in the Intervention group, = 0 otherwise $e_{it} \sim N(0, \sigma^2)$ β_{3A} is the mean difference in Physical Summary Score change between the Intervention and usual care groups. The coefficient β_{2A} allows for mean differences in Physical Summary Scores between groups at baseline. The coefficient β_4 allows the change in Physical Summary Score to depend on initial level.

Postoperative falls

Chi square test will be used to compare the incidence of falls at 12-months postoperatively between patients in the EEG-guided and in the usual care groups.

iii) Explore whether a multi-component safety intervention is associated with improved patient reported health-related quality of life and decreased incidence of postoperative falls (Aim 3 in Figure 2)

We will design a prospective matched cohort study using the ENGAGES participants (received multi-component safety intervention) and SATISFY-SOS patients who are not enrolled in the ENGAGES study (did not receive multi-component safety intervention). Participants in the ENGAGES study will be matched with reference subjects according to preoperative characteristics. Reference subjects will be identified through the ongoing SATISFY-SOS cohort, and will be matched by age (± 1year), American Society of Anesthesiologists' physical status (1 to 4), type of surgery (cardiac vs non-cardiac), date of planned surgery (± 1 year) and history of falls (yes or no). Health-related quality of life and fall incidence will be compared between these matched cohorts at approximately 1 month and 1 year postoperatively.

All statistical analyses will be performed using SAS, version 9.4 (SAS Institute, Inc., Cary, North Carolina). All

tests will be two-sided and by arbitrary convention[105] will be considered statistically significant at a p<0.05, and all results will be presented with estimates and 95% confidence intervals. However, based on the uncertain prior probability (plausibility) of the alternative hypothesis[106] (i.e., EEG guidance of anesthesia decreases postoperative delirium) and concerns raised about lack of reproducibility in science[107,108], a statistically significant result with a p value just <0.05 should be considered as preliminary, and future studies should be conducted for corroboration. A more stringent p value (e.g., p<0.005) would be required to conclude that subsequent studies would be very likely to reproduce these results with a p value <0.05.[109] Apart from statistical significance, the ultimate decision regarding the routine implementation of EEG-guidance of general anesthesia in preventing postoperative delirium will also depend on the estimated effect size of this intervention.

Sample Size Calculations

All sample size calculations have been performed using SAS PROC POWER.

i) Decrease in Delirium

Our sample size calculations are based on the anticipated delirium incidence and effect size for our primary endpoint analysis. Based on results of a previously published meta-analysis of four studies investigating the use of BIS-guided anesthetic administration, we conservatively assume an incidence of postoperative delirium in the routine anesthesia care group of 25%.[29] We performed a sample size sensitivity analysis and calculated different scenarios with different values for the delirium incidence in the intervention arm and corresponding power (80%, 90%, and 95%). With a two sided alpha <5% and 1,232 patients (616 per arm), the trial will have >95% power to detect an absolute decrease in delirium incidence ≥9%, >90% power to detect a decrease in delirium incidence ≥8%, and >80% power to detect a decrease in delirium incidence ≥7%. With a 7% decrease in delirium incidence, the 95% confidence interval would be approximately 3% to 12%. Even a 3% decrease in delirium incidence would be clinically important, suggesting that delirium would be prevented in one out of every 33 at risk patients who received EEG-guidance of general anesthesia.

ii) Health Related Quality of Life

The overall sample size of our study is defined through estimations of the primary outcome (delirium). For secondary analyses, we assume that ~80% of our trial population (~1,000 participants) will have completed the trial and the 1-year follow-up survey. With this sample size of 1,000, we can detect a difference of 0.5 points (standard deviation of 2.5) in the mean change of Physical Health Score from baseline to 1 year between the intervention and usual care group with a power of >80% and a two-sided alpha level of p<0.05.

iii) Postoperative Falls

This calculation is similarly based on the assumption that ~80% of our trial population (~1,000 participants) will have completed the trial and the 1-year follow-up survey. Based on a study that showed a preoperative fall prevalence of 33% over six months preoperatively in a similar patient population to the ENGAGES trail, we will conservatively assume an incidence of postoperative falls at 1-year in the routine anesthesia care group of 40%.[110] With a sample size of 1,000, we will have >80% power to detect an absolute risk reduction of 12% between the EEG-guided and the usual care group at a two-sided alpha level of p<0.05.

Analysis of Pragmatic Elements of the ENGAGES Study

According to seven of nine criteria elaborated in the pragmatic–explanatory continuum indicator summary (PRECIS-2) tool[111], the ENGAGES trial is designed predominantly as a pragmatic rather than as an explanatory study (see Figure 6). 1) Regarding eligibility criteria, all surgical patients older than 60 undergoing major surgical procedures are eligible for the ENGAGES study, regardless of other known risk factors for delirium. As such, this is broadly representative of a substantial population of older surgical patients. However, the results would not apply to younger patients or to older patients undergoing non-invasive surgical procedures. 2) Patients are recruited in usual clinical settings with slightly more effort made over and above what would be used in the usual care setting to engage with patients. 3) The trial is being conducted in usual care settings, predominantly in the operating rooms and in hospital wards. 4) Any anesthesia practitioner, regardless of their background or expertise in EEG monitoring, can apply the EEG-guided protocol. However, during the first phase of the study, there will be structured education of clinicians to increase their familiarity

and comfort with EEG-guidance of anesthesia. We therefore anticipate that practitioner familiarity with EEG will increase over the course of the study, although only basic knowledge regarding EEG analysis will be needed. Similarly, any anesthesia practitioner, regardless of their background or expertise, can apply the control (comparison) protocol. 5) Instructions on how to apply the EEG-guided protocol are flexible, offering practitioners discretion in deciding how to formulate and apply it. Although clinicians carrying out the EEG-guided protocol will use their own discretion in managing anesthesia, there is an expectation that less anesthesia will be administered in the EEG-guided arm and that the cumulative duration of EEG suppression will be less in the EEG-guided arm. During the first phase of the study, clinician adherence to the EEG-guided protocol will be evaluated and will partially inform the value of proceeding with the second phase of the study. Similar to the intervention arm, when patients are randomized to the control arm, anesthesia clinicians will have leeway to pursue their usual practice with minimal restrictions. There are some limitations in relation to anesthetic technique (e.g. based on potent volatile anesthetic), however these are consistent with current practice at our institution and more broadly. 6) For the primary intervention of the ENGAGES trial, participants will be anesthetized and will have no ability to impact adherence to the intervention. Therefore, this domain was left blank in the PRECIS-2 determination, as recommended[111]. 7) Patients enrolled to the ENGAGES trial will be followed with more frequent visits and more extensive data collection than would occur in routine practice. 8) Incident delirium, the primary outcome of the study, is an objectively measured, clinically meaningful outcome to the study participants. The outcome can be assessed under usual conditions and typically does not rely on central adjudication. However, special training in rigorous delirium assessment is required. It is important to note that the abstraction of information of delirium from the medical records bolsters the pragmatic aspects of the trial, since this is an information source that is readily available at any hospital. 9) The analysis of the results will include all patients regardless of clinician compliance with the EEG-guided protocol (i.e. it will be an "intention-to-treat" analysis). The analysis will attempt to determine whether or not the EEG-guided protocol prevents postoperative delirium under the usual conditions, with all the noise inherent therein. Although in most respects the ENGAGES trial was judged to be pragmatic, this appraisal might have been biased as it was conducted by investigators associated with the study.[112]

Figure 6 shows the design elements of the ENGAGES trial that tend to be pragmatic (markers placed towards the periphery) and elements that tend to be explanatory (markers placed towards the center).[111,113] This figure was generated from a median determination for each criterion (using a 1 to 5 ordinal scale from explanatory to pragmatic) from 18 independent raters on the study team. Aside from the intensity of patient follow-up and the expertise needed to deliver the EEG-guided protocol, the ENGAGES study fulfills the criteria for a pragmatic clinical trial.[111,112]

Strengths and Limitations

The ENGAGES study has important strengths. It is largely a pragmatic randomized clinical trial conducted in a high volume, real world clinical setting that incorporates an easy-to-implement intervention and examines an outcome that is of tremendous importance to patients, healthcare providers and society. The ENGAGES study can be conducted efficiently as many components of the proposed study are incorporated into existing infrastructures and processes at Washington University: 1) enrollment will be integrated into the flow of the Center for Preoperative Assessment and Planning; 2) the conduct of the study will largely be by anesthesiologists and certified registered nurse anesthetists in the course of their routine clinical work; and 3) most of the follow-up data will be obtained from SATISFY-SOS, an ongoing registry study. Randomization can be implemented easily at the point of patient care, as the anesthesia protocols do not require any lead-in time or advanced preparation. The study will enroll older patients, who are recognized to be vulnerable and under-studied in clinical research. This targeted population is especially important to understand and would stand to benefit significantly from reductions in postoperative delirium and related outcomes. The secondary outcomes of the study include patient-reported health-related quality of life, which is extremely relevant to patients. The study is also designed to detect postoperative falls and their potential prevention. The trial will exploit the extensive SATISFY-SOS prospective patient registry and our highly evolved perioperative electronic medical record. Most of the data collected for the trial will use existing infrastructure, and additional data will be entered

using the REDCap resource that integrates well with our other data repositories. The feasibility of the trial is enhanced by participation of a multi-disciplinary team of investigators that has now established a track record of collaboration and completion of major clinical trials. As the intervention is inexpensive and straightforward, if the results of the study show compelling effectiveness, it will be logistically simple to implement and sustain the EEG-guided anesthesia protocol at our institution and disseminate it nationally in the United States.

The following limitations should be considered. A single clinical trial should seldom be regarded as definitive. As there is no clear estimate for the prior probability that EEG guidance of anesthesia prevents postoperative delirium, if the results of this trial do suggest that EEG-guidance of anesthesia might decrease delirium at the arbitrary statistical threshold of $p<0.05$, it will be necessary to replicate this finding in future studies. On the other hand, even if the study finds a non-significant (at the arbitrary threshold of $p>0.05$) decrease in delirium in the EEG-guided group, it is likely that follow-up studies will be warranted to clarify whether or not there is a clinically meaningful reduction in delirium with EEG-guidance of anesthesia, and whether there are specific patient populations that might especially benefit from this intervention. If EEG-guidance of anesthesia can prevent postoperative delirium, demonstrating its effectiveness will depend on clinicians' adherence to the protocol. However, the inability to blind clinicians to the trial allocation group is a potential source of bias and confounding. We are attempting to confirm that clinicians do alter anesthetic management based on the intervention during the pilot phase of the study. The inclusion of patients in a clinical trial focused on the prevention of delirium, and the provision of practical educational information to patients and family members could decrease the incidence of postoperative delirium. Furthermore, if the multi-component intervention is successful in preventing falls and in improving quality of life, this could curtail our ability to detect an impact of the EEG-guided anesthetic protocol on these outcomes. In addition to the pragmatic structured chart review, there are two clinical assessment methods that will be used to diagnose delirium: the CAM-ICU and the CAM. The CAM-ICU is less sensitive than the CAM, but is the only instrument that has been validated for patients who are non-verbal (i.e., with a breathing tube or tracheostomy in place). Based on our institutional data, the vast majority of patients enrolled in the in the study will be extubated within the first two postoperative days. Therefore, most patients will have delirium assessments with the CAM, which is the more sensitive and specific instrument. We will also test whether intubation status modifies the result in secondary analysis. The study design includes a 30-day and a 1-year follow up for patient reported outcomes, and incomplete follow-up is therefore a potential limitation. Based on our previous B-Unaware and BAG-RECALL studies,[40,41] we are confident that we can achieve a 30-day follow up rate of >90%. In our SATISFY-SOS cohort, the 1-year follow up has yielded approximately 66% response rate. We have performed sensitivity analysis in our power calculations and have taken into account this potential attrition in our methods. Furthermore, we plan to enhance follow-up by using supplementary phone calls from members of the study team. As delirium is a fluctuating disorder, there is a risk that it can be missed by periodic assessments. We are attempting to mitigate this by assessing patients for delirium during a time of day (afternoon/evening) when delirium occurs more commonly. Furthermore, we are incorporating structured chart review, which has been validated as a complementary approach that increases the detection of delirium.[93,94]

Potential Benefits, Risks and Alternatives

Benefits

If the hypotheses motivating this study are correct, patients who are randomized to receiving EEG-guidance of anesthesia will have a lower chance of experiencing postoperative delirium and possibly also its downstream consequences, including quality of life decrement and injurious falls. All the patients enrolled in this study will potentially benefit from the safety interventions intended to decrease the likelihood of postoperative falls.

Risks

The risks associated with this study are low. There is a rare risk of breach of confidentiality. The main risk attributable to the EEG-guided intervention might be increased risk of intraoperative awareness. This is unlikely as previous studies that have randomized patients to EEG-guidance have not found an increased incidence of awareness with EEG-based anesthetic protocols.[40-42] However, limitations of the BIS in detecting awareness in the presence of neuromuscular blocking agents have recently been highlighted.[114] Titration of anesthesia in the

ENGAGES trial is therefore based primarily on the raw EEG waveform and only secondarily on the processed EEG index. Nonetheless, as a potential safety concern regarding the EEG-guided intervention remains that it could increase the incidence of intraoperative awareness, this outcome will be tracked postoperatively with a modified Brice interview[115] conducted within 48 hours of extubation. In addition, questions regarding intraoperative awareness are also included in the SATISFY-SOS 1-month survey. A data-safety monitoring committee will review adverse events with the PI and, in consultation with the institutional review board, might recommend stoppage of the trial if awareness events appear to be increased in the intervention group. As part of the informed consent process for this study, patients will be informed of the rare risk of awareness. In the unlikely event that serious side effects occur, they will be documented and will be reported to the human research protection office and to the study's data safety monitoring board. Participants will not incur any study-related expenses, nor will they be financially compensated for their participation.

Minimization of Risks and Confidentiality

Necessary protected health information will only be shared with members of the research team. To help protect confidentiality, research charts will be stored in a locked cabinet inside the locked research office. Electronic data and demographic information will also be kept in a password-protected electronic database stored on the departmental network drive only accessible via password-protected departmental computers. A member of the research team will enter this information. Only code numbers will appear on any data and documents used for evaluation or statistical analyses. Patients may choose not to participate in this study and there will be no penalty in terms of the care that they receive.

The Division of Biostatistics Informatics Core at Washington University will be used for data processing and management. Washington University belongs to a consortium of institutional partners that work to maintain a software toolset and workflow methodology for electronic collection and management of research and clinical trial data. REDCap (Research Electronic Data Capture) data collection projects rely on a thorough study-specific data dictionary defined in an iterative self-documenting process by all members of the research team with planning assistance from the Division of Biostatistics Informatics Core. The iterative development and testing process result in a well-planned data collection strategy for individual studies. REDCap servers are securely housed in an on-site limited access data center managed by the Division of Biostatistics at Washington University. All web-based information transmission is encrypted. The data is all stored on a private, firewall-protected network. All users are given individual user identifiers and passwords and their access is restricted on a role-specific basis. REDCap was developed specifically around HIPAA-Security guidelines and is implemented and maintained according to Washington University guidelines. REDCap currently supports >500 academic/non-profit consortium partners on six continents and 38,800 research end-users.

Adverse Event Reporting and Safety Monitoring

The research team will monitor the study for adverse events. All serious adverse events (SAEs) will be reported to the IRB according to IRB stipulations. The monitoring plan for this study is appropriate for the planned pragmatic trial. We have already conducted three large clinical studies including approximately 28,000 patients, half of whom received general anesthesia with EEG-guidance. There were no adverse events attributable to EEG-guidance of anesthesia in these studies[40-42]; it is unlikely that there will be adverse events attributable to EEG-guidance in the ENGAGES study.

The ENGAGES has an appropriate data and safety monitoring plan for a low risk clinical trial. There is a charter to guide the functions of the DSMB, and the DSMB will produce reports in accordance with NIH guidelines. The DSMB will provide independent oversight of the ENGAGES Clinical Trial, and will review general conduct of the trial and study data for participant safety.[116] The DSMB is comprised of independent, multidisciplinary experts who will make recommendations regarding the continuation, modification, or termination of the trial.[117] The members will have the requisite expertise to examine accumulating data, to protect the integrity of the clinical experiments to which the patients have consented to participate, and to assure the regulatory bodies, the public and the NIH that conflicts of interest do not compromise either patient safety or trial integrity.[118] The DSMB will convene twice annually to review safety events. There will be a provision for early stoppage for safety concerns, but not for efficacy or for futility.[116] Trials that stop early for

benefit show implausibly large treatment effects, particularly when the number of events is small.[119] Truncated trials have been associated with greater effect sizes than trials not stopped early, independent of the presence of statistical stopping rules.[120] The members of the DSMB shall have no direct involvement in the conduct of the ENGAGES study. Neither shall they have financial, proprietary or professional conflicts of interest, which may affect the impartial, independent decision-making responsibilities of the DSMB.[116,117] All DSMB members have signed a Conflict of Interest Certification to confirm no conflict exists. There are five people on the DSMB, in order to optimize performance.[121] The DSMB will be advisory rather than executive on the basis that it is the ENGAGES study investigators in partnership with the National Institute on Aging who are ultimately responsible for the conduct of the trial (see Figure 7).[121]

Figure 7: ENGAGES trial organization

Premature Study Termination

Patients in the EEG-guided anesthetic group will, on average, receive decreased concentrations of inhaled anesthetic agents during their surgeries. Reduction of anesthetic administration using simultaneous EEG-based monitoring of anesthetic depth has been previously described without reports of increased intraoperative awareness.[27,122] However, it is theoretically plausible that a significantly higher rate of awareness events could occur in a cohort that on average receives lower anesthetic concentrations. Therefore, we propose comparing the incidence of intraoperative awareness reports in the EEG-guided and usual care groups. We will recommend to the DSMB that this occur after 600 patients have been enrolled. A one-tailed comparison will be used to compare the incidences of awareness in the groups, and consideration should be given to terminating the study if the EEG-guided cohort has a significantly greater incidence of intraoperative awareness compared with the standard of care group with a p value <0.05. In making recommendations, the DSMB could take into consideration the severity of the awareness experiences, including reports of pain, paralysis and distress.[123] Apart from intraoperative awareness, it is not currently hypothesized that decreased anesthetic administration is associated with clinically relevant adverse outcomes (e.g. death, myocardial infarction, stroke). It is possible that decreases anesthetic administration might be associated with intraoperative patient movement, or with increased intraoperative blood pressure and heart rate. However, these are surrogate measures with unclear clinical relevance, which should not therefore impact a decision to terminate the study early.

We recommend to the DSMB not performing an interim analysis of delirium rates for any consideration of termination. Currently available data support the possibility that an EEG-guided anesthetic management to reduce anesthetic administration might decrease the incidence of postoperative delirium or have no effect on this outcome.[26-29] Conversely, the possible finding of a higher incidence of delirium in the EEG-guided cohort would conflict with current evidence. When interpreted in the context of existing evidence, the finding of significantly disparate incidences of postoperative delirium in a partially completed ENGAGES trial would not provide a sufficient evidence base to change the standard of practice for anesthetic guidance of these patients.

Indemnity

Washington University School of Medicine is responsible for any non-negligent damage incurred as a result of participating in the ENGAGES Trial. The indemnity is renewed on an annual basis. Washington University School of Medicine assures that it will continue renewal of the indemnity for the duration of the trial.

Ethics and Dissemination

The trial steering committee will be responsible for all major decisions regarding changes to the protocol. The committee will communicate these changes to the IRB and appropriate parties. The final trial dataset is the property of the investigative team and shall not be shared without permission from the principal investigator. Data will be shared with the National Institute on Aging. Dissemination plans include presentations at local, national and international scientific conferences. Every effort will be made to publish results of the ENGAGES trial in a peer-reviewed journal. Dissemination of results to study participants and their family members will be available upon request. Updates and results of the study will be available to the public at clinicaltrials.gov.

Addendums

Pre-Specified Sub-Studies

a) *Duration and Severity of Delirium*
In addition to the incidence of delirium (the primary outcome of the ENGAGES study), other outcomes of interest will be the duration of delirium and the severity of delirium, both of which have been shown to have prognostic importance.[124-128] The severity of delirium will be scored using the CAM-Severity (CAM-S) metric, which has specifically been shown to be strongly associated with clinically relevant outcomes.[128] Delirium will also be assessed postoperatively on the day of surgery, when patients are sufficiently awake (RASS > -4).

b) Agreements among the FAM-CAM, researchers' delirium assessments and patient perceptions
The ENGAGES study is a patient-centered study. As such, the active involvement of patients and their families is an important component. The Family Confusion Assessment Method (FAM-CAM) instrument has previously been shown to have good agreement with the CAM and with DSM-IV diagnostic criteria in patients with cognitive impairment and in hospitalized patients.[103,104] The utility of the FAM-CAM has not been established in postoperative patients; however it has been successfully implemented in the postoperative setting in the ongoing PODCAST clinical trial.[129] Patients will also complete a delirium self-assessment questionnaire (Appendix). Both the FAM-CAM assessments and the patients' self-assessments will be compared with the researchers' delirium assessments.

c) Duration or recurrence of delirium after hospital discharge as measured by the FAM-CAM and patient perceptions
Little is currently known about either duration of delirium or recurrence of delirium after hospital discharge in postoperative patients. The FAM-CAM and patient self-reports will be used to assess these outcomes.

d) Clinically relevant outcomes associated with delirium
Delirium incidence, duration and severity have all been shown to be associated with other (downstream) clinically relevant outcomes, including mortality, length of ICU stay, length of hospital stay, falls, cognitive decline and functional decline. In the ENGAGES study, these associations will be explored. The data on downstream outcomes will be obtained from hospital records or from patient reported outcomes measures that are collected as part of the ongoing SATISFY-SOS study.

e) Comparison of patient-reported and observational pain scores
It is likely that patients with delirium are less able to convey verbally the extent to which they are in pain.[130] Given that postoperative delirium is common and may relate to uncontrolled pain, this has important implications for the assessment and treatment of postoperative pain. We plan to compare patient reported and behavioral pain assessments in both non-delirious and delirious patients.[130] (See Appendices for pain assessment instruments)

f) Postoperative actigraphy and EEG
Postoperative disturbances in sleep and EEG abnormalities have previously been associated with postoperative delirium.[131-134] EEG data will be collected from some patients at around the time of delirium assessments. Patients might also wear actigraphy watches to help distinguish episodes of sleep from wakefulness in the postoperative period.[135]

g) Relationship between clinical CAM-ICU and rigorous delirium assessments
Routine clinical (i.e. conducted by ICU nursing staff) delirium assessments in the intensive care units (conducted with the CAM-ICU) will be collected when these are available. Comparison will be made between these routine clinical assessments and the assessments made by the research team.

h) *Association Between Delirium and Patient Outcomes*
The ENGAGES study will be evaluate the association between postoperative delirium and patient reported outcome metrics, including quality of life and falls, up to one year postoperatively.

i) *Postoperative outcomes hypothesized to be associated with anesthetic depth*
It is likely that patients randomized to the EEG-guided protocol will be exposed to lower concentrations of anesthetic agents, and on average will not be as deeply anesthetized. There is an ongoing randomized, clinical trial investigating the effects of depth of anesthesia on a range of outcomes[101,102], including death, myocardial infarction, cardiac arrest, pulmonary embolus, stroke, surgical site infection, ICU length of stay, hospital length of stay, intraoperative awareness, persistent pain and cancer recurrence. Many of these outcomes are tracked with the SATISFY-SOS study, and will therefore be reported for patients enrolled in the ENGAGES study.

j) *Delirium Prediction Models*
It is important to improve our understanding of factors that are associated with an increased incidence of postoperative delirium or perhaps may even mediate an elevated risk for postoperative delirium. Previous studies have explored risk factors, usually using logistic regression models.[29,136-148] In a previous study we used a Bayesian exploratory approach with a stochastic search variable selection method.[29] The ENGAGES study will rigorously assess a large number of surgical patients for postoperative delirium, and it will therefore lend itself to further exploration, refinement of risk models and hypothesis generation. Based on results from previous studies, we will include specific variables in our analyses. Patient age, demographic, life style and comorbidity information will be assessed at baseline through a standardized interview in the CPAP clinic. Data on previously described risk factors for postoperative delirium will be acquired including: history of postoperative delirium, modified Charlson Comorbidity Index, American Society of Anesthesiologists' Physical Status, functional status, level of education, olfaction, baseline cognition, depression (using the PHQ-9 questionnaire), indices of frailty, obstructive sleep apnea, baseline hematocrit, baseline sodium and creatinine, preoperative psychoactive medications (e.g. opioids, benzodiazepines, sedatives, clonidine), alcohol use, dosages of perioperative medications (e.g. hypnotic anesthetics, opioids, benzodiazepines, dexmedetomidine), intraoperative hemodynamic parameters, other physiological parameters, processed EEG indices (e.g. BIS, burst suppression), vasoactive medications, perioperative blood transfusions, postoperative mechanical ventilation, postoperative pain (using visual analogue scale and behavioral pain scale), postoperative sleep deprivation, postoperative medical complications, postoperative shock, postoperative anemia (hematocrit <30%), postoperative hypoalbuminemia (albumin <3 g/dL), postoperative temperature, and postoperative sodium concentration.[29,79,136-148]

Collaborations with Other Studies

The ENGAGES study is being conducted in collaboration with complementary trials at the University of California, San Francisco (UCSF) (NCT01983384) and the University of Manitoba in Winnipeg. Some of the outcomes will be analyzed considering data from some or all of these studies, as appropriate. In terms of the practicality of disseminating the EEG-guided protocol in North America and beyond, it will be important to demonstrate the feasibility and impact of the protocol in multiple sites.

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Authorship Eligibility and Contributorship

Authorship for this study will be given to key personnel involved in study design, recruitment, data collection, and data analysis. There are no publication restrictions and no professional writers will be involved in the generation of the manuscript. M. Avidan, D. Emmert, K. Escallier, B. Fritz, T. Graetz, R. Huneke, S. Inouye, E. Jacobsohn, E. Lenze, J. Leung, N. Lin, S. Melby, B.J. Palanca, E. Schmitt, S. Stark, T. Stevens, B. Torres, P. Vlisides, T. Wildes, and A. Winter are responsible for conceptualizing study design. S. McKinnon managed patient safety protocol and IRB compliance. H. Maybrier, A. Mickle, M. Muench, M. Murphy, and R. Upadhyayula were responsible for recruitment, enrollment, data collection, and editing the protocol. M. Avidan is responsible for drafting the protocol.

All authors including Avidan, Emmert, Escallier, Fritz, Graetz, Huneke, Inouye, Jacobsohn, Lenze, Leung, Lin, Maybrier, McKinnon, Melby, Mickle, Muench, Murphy, Palanca, Schmitt, Stark, Stevens, Torres, Upadhyayula, Wildes, and Winter have critically revised the ENGAGES protocol and approved the final version. All authors agree to be accountable for the accuracy and integrity of all aspects of the ENGAGES trial.

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Competing Interests

None of the authors has conflicts of interest to disclose.