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Ability of postoperative delirium to predict intermediate-term postoperative cognitive function in patients undergoing elective surgery at an academic medical center: protocol for a prospective cohort study

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Short title: Postoperative delirium predicting intermediate-term post-operative cognitive function

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1. Abbreviations and Definitions of Key Terms

POD – Postoperative delirium

POCD – Postoperative cognitive decline

EEG – Electroencephalography

ENGAGES - Electroencephalography Guidance of Anesthesia to Alleviate Geriatric Syndromes

STATISFY-SOS – Systemic Assessment and Targeted Improvement of Services Following Yearlong Surgical Outcomes Surveys

STROBE – Strengthening The Reporting of Observational studies in Epidemiology

ASA – American Society of Anesthesiologists

CPAP – Center for Preoperative Assessment and Planning

2. Introduction

This protocol followed published guidelines for protocols for observational studies, as well as the STROBE checklist for cohort studies.[1, 2] For maximum transparency, we also added sections addressing additional sub-analyses and limitations. This protocol is version 01, written on 03/01/2017.

3. Abstract

Introduction: Postoperative delirium is a common complication in elderly patients, characterized by a fluctuating course of altered consciousness, disordered thinking and inattention. Preliminary research has linked postoperative delirium with persistent cognitive impairment and decreased quality of life. However, these findings maybe confounded by patient co-morbidities, postoperative complications, and frailty. Our objective is to determine whether postoperative delirium is an independent risk factor for persistent impairments in attention and executive function in patients undergoing elective surgery. Our central hypothesis is that patients with postoperative delirium are more likely to have declines in cognitive function and quality of life one year after surgery compared with patients without postoperative delirium. We aim to clarify whether these associations are independent of potentially confounding factors. We will also explore the association between postoperative delirium and incident dementia.

Methods and Analysis: This study will recruit 200 patients from the ongoing Electroencephalography (EEG) Guidance of Anesthesia to Alleviate Geriatric syndromes (ENGAGES) study. Patients who live ≤45 miles from the study center or have a planned visit to the center 10-16 months postoperatively will be eligible. Patients with postoperative delirium will be compared to patients without delirium. The primary outcome of cognitive function, and secondary outcomes of quality of life and incident dementia will be compared between cohorts. Cognitive function will be measured by Trails A&B and Stroop Color Word Test, quality of life with Veteran's RAND 12-item Health Survey, and incident dementia with the Short

Blessed Test. Multivariable regression analyses and a Cox proportional hazards analysis will be performed. All results will be reported with 95% confidence intervals and α=0.05.

Ethics and Dissemination: This study is approved by the ethics board at Washington University. Plans for dissemination include scientific publications and presentations at scientific conferences.

Trial registration: This observational study is a pre-specified sub-study of ENGAGES (NCT02241655).

Strengths and Limitations of this study:

Strengths:

- Postoperative intermediate term cognitive function and quality of life are important patient-centered outcomes.
- Analysis will include salient patient characteristics, including preoperative cognition, comorbid conditions and frailty.
- Study sample will consist of an understudied population in clinical research.

Limitations:

- Potential for loss to follow-up and non-response bias
- Since this is an observational study, we cannot establish a causal relationship between postoperative delirium and persistent declines in cognition and quality of life.
- We cannot determine whether cognitive function deviates from the pre-operative trend, without multiple preoperative cognitive assessments to establish a trajectory.

4. Background

Since Bedford's 1955 case series suggesting an association between surgical intervention and cognitive impairment, there has been growing concern among the public that cognitive decline is a common consequence of surgery.[3] This pervasive view continues to concern patients and their families, fueled by anecdotal evidence and media coverage. Postoperative cognitive decline (POCD) has been a growing topic for scientific investigation after several studies were published by the International Study of Post-Operative Cognitive Dysfunction (ISPOCD) group. While several influential studies demonstrated early postoperative cognitive decline (POCD) lasting up to 3 months, the persistence of this cognitive decline has been controversial.[4-8] Importantly, the population of Americans older than 60 years is projected to double over the next 30 years,[9] and many will require surgery. Acute and long-term cognitive changes related to surgical intervention are particularly distressing to patients and their families. Therefore, clarification of cognitive outcomes would assist patients and practitioners in making an informed decision about the relative risks and benefits of proceeding with elective surgery.

4.1 Literature search and review

A systemized literature review was conducted with the help of a librarian experienced in systemic review (see Acknowledgement). Ovid Medline was searched for studies published between 1981 and September 2016 using the query: Postoperative or after surgery AND Delirium AND Cognitive function or dementia AND Elderly AND Long-term or intermediate term or follow up or cohort studies or retrospective studies. Articles in English or with English translation were considered. JC and RT reviewed the 301 search results and found 28 articles that were relevant to our clinical question. 21 out of the 28

relevant articles (84%) showed significant result in the relationship between postoperative delirium (POD) and intermediate- to long-term cognitive decline. These seem to suggest a high pre-test probability in studying the ability of POD to predict intermediate-term cognitive decline. However, these studies are heterogeneous in the study design, selected surgical patient population, and outcome measurement tools complicating synthesis of the systemic search to draw conclusions.

POD is a common complication for surgical patients over the age of 60 years.[10] It is a neurological syndrome characterized by a combination of features, which can include an acute change, fluctuating course, disordered thinking, altered consciousness and inattention. Although usually transient, POD has been associated with several salient adverse outcomes, including mortality, prolonged ICU stay and persistent cognitive decline.[11-14] One prospective cohort study of cardiac surgery patients suggested patients experiencing POD had prolonged cognitive impairment at one year.[14] However, after adjusting for baseline differences in cognitive function, there was no significant difference compared with controls. The same study also demonstrated that mild cognitive impairment preoperatively may predispose patients to delirium; thus POD may be exposing patients who are already experiencing sub-clinical cognitive decline or those who have an underlying vulnerability to cognitive decline. Another study, in orthopedic surgery patients found no association between POD and cognitive decline at three months.[15] There are few articles addressing the association between POD and persistent postoperative cognitive decline (arbitrarily defined as lasting >6 months). A prospective matched controlled survey with an average of 30-month follow-up demonstrated that dementia or mild cognitive impairment was diagnosed in 77.8% of the surviving hip surgery patients with POD, almost doubling the 40.9% rate of control patients (relative risk = 1.9, 95% CI = 1.1-3.3). However the study was underpowered to evaluate the long-term cognitive function, as the power calculation was based on the original study and no intermediate assessments were made to track patients' cognitive function.[16] Overall, the results of these studies suggest an association between POD and persistent cognitive impairment, however compelling data supporting an independent association are lacking.

In addition to cognitive outcomes, quality of life and functional capacity are also important patient-centered outcomes that require further investigation. While one study found that elderly surgical patients tended to have long-term cognitive and functional decline compared to non-surgical patients,[17] few studies have examined the association between cognitive function and quality of life or activities of daily living. One prospective study over a 10-month period demonstrated that delirium was an independent risk factor for becoming dependent for personal activities of daily living after ICU discharge (OR = 2.188, P <0.046) and that patients with POD also demonstrated a greater decline in Short-Form-36 domains after discharge, especially in physical function, vitality, and social function.[18] However, this study could not draw conclusions regarding cognitive function due to lack of data. Kastaun et al. reported perceived impairment in ability to perform activities of daily living one year after surgery, however did not detect significant cognitive decline at that time.[19] It remains unclear whether cognitive decline results in impaired functional capacity or decreased quality of life. In fact, given the variable definitions of POCD, data from previous studies are difficult to interpret. As many of the deficits found in neuropsychiatric testing are subtle, it is possible that detected cognitive impairment has no clinically significant impact on these patient-centered outcomes. Instead of using an arbitrary threshold to dichotomize cognitive function as normal or impaired, it would be more informative to correlate these outcomes with cognitive function as a continuous variable or stratified into multiple groups.

4.2 Justification

The population of older adults is projected to double over the next thirty years, and many will undergo elective surgery with the hope of overall improvement in health and quality of life. Postoperative delirium is a common and potentially preventable complication, thus clarification of its association with persistent declines in cognition and quality of life will inform perioperative care. Prior studies have not demonstrated an association independent of pre-existing patient characteristics and perioperative course. The proposed study addresses the methodologic concerns in current literature by: 1. objectively evaluating attention and executive function with validated cognitive tests, 2. obtaining measurements of baseline cognitive function, 3. conducting statistical analysis which includes important potential confounding factors including frailty measures, and 4. sampling from an unselected surgical population. The results of this study will contribute to the broader understanding of postoperative cognitive changes, and may help identify and provide therapies for susceptible patients earlier to ultimately improve outcomes.

As part of the ENGAGES study, patients have been enrolling since January 2015, with 804 patients enrolled thus far. Over the last year, the ENGAGES research team has enrolled approximately 35 patients per month, and has gathered baseline cognitive data on a majority of participants. Preliminary screening suggests about 65% of those enrolled in ENGAGES are eligible for the current study. Anticipating that half of those contacted will enroll, we expect to assess 10 to 15 patients per month. The scaffold of ENGAGES and trained study members make this sub-study highly feasible.

5. Specific Aims

Specific Aim #1: Determine whether patients who experience postoperative delirium perform worse on specific cognitive tests at approximately one year after surgery.

We hypothesize that postoperative delirium is independently associated with poorer performance on tests of attention and executive function at one year after surgery. We will conduct a regression analysis, including likely contributory variables, to assess the association between delirium and cognitive decline at approximately one year.

Specific Aim #2: Evaluate whether patients who experience postoperative delirium have worse quality of life at approximately one year postoperatively.

We hypothesize that postoperative delirium is independently associated with decreased quality of life one year after surgery. We will conduct a regression analysis, including likely contributory variables, to assess the association between delirium and health-related quality of life at approximately one year.

Specific Aim #3: Explore whether patients who experience postoperative delirium are more likely to develop dementia within approximately one to two years of their surgery.

We hypothesize that postoperative delirium is independently associated with incident dementia one to two years after surgery. We will conduct a Cox proportional hazards regression, including likely contributory variables, to assess the rate of incident dementia approximately one to two years after surgery.

6. Study Design:

This prospective cohort study is pre-specified sub-study of the ENGAGES study. The ENGAGES study is a randomized clinical trial enrolling approximately 1,200 patients sixty years and older who will undergo elective major surgery at Barnes Jewish Hospital (BJH), St. Louis, MO.

The parent trial will recruit patients primarily from the Center for Preoperative Assessment and Planning (CPAP) clinic. Among inclusion criteria for ENGAGES, details of which have been previously published,[20] is enrollment in the Systematic Assessment and Targeted Improvement of Services Following Yearly Surgical Outcomes Surveys (SATISFY-SOS) study. As part of ENGAGES, participants will complete a comprehensive baseline assessment including cognitive tests, frailty measures, and screening for delirium and dementia. Postoperatively, patients will have daily evaluations for delirium during the hospital stay. The current study will retrospectively identify 200 participants who reside within approximately 45 miles from the hospital or those who have a planned visit to the hospital between ten to sixteen months post-operatively. Patients diagnosed with delirium postoperatively will be compared to those without delirium. A prospective intermediate-term postoperative assessment will be conducted by a research team member blinded to whether the patient developed postoperative delirium.

7. Study Groups

The target population for this study is patients who underwent preoperative assessment for elective surgery at the Center for Preoperative Assessment and Planning (CPAP) clinic at Barnes Jewish Hospital (BJC) in St. Louis, Missouri. The ENGAGES study is enrolling 1,232 patients who are already enrolled in the STATISFY-SOS study. Inclusion criteria include patients sixty 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 two days postoperatively (i.e., 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). The ENGAGES study has minimal exclusion, as there are no absolute contraindications to EEG monitoring. Exclusion criteria include neurosurgical procedures, preoperative delirium, patients who are unable to participate adequately in delirium screening, including those who are blind, deaf, illiterate, or not fluent in English, patients with a history of intraoperative awareness during intended general anesthesia, and patients who had a second surgery planned within five days after the index surgery. This prospective study will enroll 200 patients who are already enrolled in the ENGAGES and SATISFY-SOS studies. In addition to previously described inclusion and exclusion criteria, participants will be included in this study if their home residence is ≤45 miles from BJH or they have a planned visit to the hospital within the specified timeframe. Patients who have not completed the baseline cognitive assessment with Trails A, Trails B and the Stroop Color Word Test will also be excluded from this study.

8. Recruitment

As part of the SATISFY-SOS study, patients have given informed consent to be contacted by Washington University for follow-up of health-related outcomes up to a year after surgery. Eligible participants will be identified by chart review and query of the ENGAGES REDCap database. A member of the research team will contact potential participants by telephone approximately ten to sixteen months after surgery for enrollment in this study. Patients may refuse participation in the study. If patients agree to

participation, written consent will be obtained when the patient comes in for assessment, prior to any data collection. Patients will then be prospectively evaluated with assessments of cognition, quality of life, and frailty measures, which are described in detail below. Meal vouchers will be provided for participation. Patients residing within approximately 45 miles of the hospital, who are willing to participate in the study, but unable or unwilling to come to the study center will be offered assessment at home by a member of the research team. Additionally, ENGAGES patients who have not completed a one-year dementia screening will be contacted by telephone approximately 18 to 24 months after surgery. Phone consent will be obtained to complete dementia screening over the telephone. Participants may refuse to participate.

9. Data

9.1 Data Collection

Routinely obtained baseline assessment in the CPAP clinic includes demographic information, a detailed medical history, surgical history, medications and physical examination. As part of SATISFY-SOS and ENGAGES, baseline assessment using the Barthel Index, Veteran's RAND 12-item Health Survey (VR-12), Eight-item Interview to Differentiate Aging and Dementia (AD-8), Short Blessed Test, alcohol sniff test, and Personal Health Questionnaire Depression Scale (PHQ8) will be performed. Baseline cognitive function will be evaluated by the ENGAGES team with the Trails A and B, and the Stroop Color and Word Test. Some patients may complete computer-based cognitive testing with the NIH toolbox at baseline (described below). Additionally, frailty will be assessed using grip strength, Timed-up and Go (TUG) test, and obtaining fall history at baseline. Participants will have daily delirium assessments by trained researchers with the Confusion Assessment Method in the postoperative period for the duration of their hospital stay. Data collected by the ENGAGES team will be entered into the Washington University School of Medicine Research Electronic Data Capture (REDCap) application. [18] Perioperative data will be retrieved from the hospital's perioperative electronic medical record (Metavision by iMDsoft®, Needham, MA). High fidelity perioperative data is routinely captured from our EMR to an SQL server (Microsoft, Redmond, WA) database. These data include bispectral index (BIS) values, EEG burst suppression durations, laboratory data, intraoperative medications, physiological readings, and postoperative recovery parameters. 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.

Cognition: The primary outcome in this study will be a composite score comprised of scores from three cognitive tests evaluating attention and executive function: Trails A, Trails B and Stroop Color Word Test. These cognitive tests will be repeated approximately one year after surgery to evaluate intermediate term cognitive function. The research team member performing the assessments will be blinded to whether the patient developed postoperative delirium. In addition to the above tests, this study proposes to use the Cognition Battery of the National Institutes of Health (NIH) Toolbox Assessment of Neurological and Behavioral Function (http://www.nihtoolbox.org). The NIH Toolbox Cognition Battery (Feinberg School of Medicine, Northwestern University, Chicago, IL), is a comprehensive yet concise standardized computer-based assessment battery; we plan to include tasks to evaluate attention (Flanker Inhibitory Control and Attention Test), episodic memory (Picture Sequence Memory Test), processing speed (Pattern Comparison Processing Speed Test), language (Picture Vocabulary), and executive function (Dimensional Change Card Sort Test and Flanker Inhibitory Control and Attention Test). Patients will have the option of completing all of the NIH Toolbox Cognition tests above, which

takes approximately 25 minutes, or an abbreviated version, which takes approximately 10 minutes to complete. The NIH Toolbox Cognition Battery has been validated for use across a wide range of ages.[21, 22] Self-reported cognitive function will be evaluated by The Patient Reported Outcomes Measurement Information System (PROMIS). PROMIS, funded by the National Institutes of Health (NIH), is a set of highly reliable, valid, flexible, precise, and responsive assessment tools that measure patient–reported health status. PROMIS v1.0-Applied Cognition-General Concerns-Short Form 4a is comprised of four questions about thinking and cognition. PROMIS v1.0-Applied Cognition-Abilities-Short Form 4a is comprised of four questions about memory. Evaluation for dementia with the Short Blessed Test will be completed for all patients at baseline, and again between one to two years after surgery.

Quality of Life: As part of the ongoing SATISFY-SOS study, patient self-reported Health-related Quality of Life information will be assessed through the VR-12 at baseline (preoperatively) and also one year after surgery. The VR-12 was derived from the Veterans RAND 36 Item Health Survey (VR-36) and contains twelve 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.[23]

Functional status: We will assess functional status with the Barthel Index for Activities of Daily Living and Lawton Instrumental Activities of Daily Living Scale. The Barthel Index is a measure of patient performance in ten activities comprised of eight questions about personal care and two questions about mobility. The Lawton Scale assesses independent living skills in 8 areas of function.

Frailty: We will measure grip strength and the Timed Up and Go (TUG) test. Grip strength will also be assessed with three measurements in the dominant hand using a Jamar® handheld dynamometer (Lafayette Instruments, Lafayette, IN). Maximal grip strength will be selected for analysis.

9.2 Data management

A customized database has been developed to facilitate data management for this study using the Research Electronic Data Capture (REDCap) system. REDCap is a secure web-based data capture system available to research groups receiving support from the Institute of Clinical and Translational Sciences at Washington University. It is maintained by the Washington University Division of Biostatistics with multiple capabilities to simplify data management and analysis. These include intuitive data entry, data audit and tracking, import of externally sourced data, and automated data export for analysis. REDCap requires unique user identification and password combinations for secure access.

10. Statistical Consideration

10.1 Sample calculations

For specific aims 1&2, continuous outcome variables will be evaluated using multivariable methods. To have a robust predictive model and prevent overfitting, it is necessary to have at least ten observations for each parameter included in the model. We plan to include ten to twelve parameters in the regression models for aims 1&2, which are specified further below. To ensure an adequate number of observations and avoid overfitting, we plan to enroll 200 patients in this study.

For specific aim 3, sample size calculation has been performed using G*POWER 3.0.10. 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 POD of 25%. For patients without delirium, we expect the rate of incident dementia to be 5%. To detect two-fold increase in the rate of dementia, with a one sided alpha <5%, unequal cohorts, and 80% power, the study would need 861 participants (215 in the delirium group, and 646 in the control group).

10.2 Statistical analysis

We will perform and report descriptive statistics (mean and standard deviation) for all variables between patients with and without the diagnosis of POD. Descriptive statistics will include chi-squared tests for categorical variables, t-tests for normally distributed continuous variables and Mann-Whitney tests for nonparametric continuous variables.

Specific Aim 1: Determine whether patients who experience POD perform worse on specific cognitive tests at approximately one year after surgery.

The primary endpoint of our analysis is cognitive function one year after surgery, as measured by the Trails A &B and the Stroop Color Word Test. Z-scores will be calculated for performance for each test, and combined to form a composite measure. Multivariable regression analysis will be used to determine whether the development of postoperative delirium is a predictor variable for cognitive function, independent from other possible contributory factors. POD will be entered as discrete numerical variable reflecting duration of symptoms. The following variables will be included in the model: age, sex, American Society of Anesthesiologists physical score, and Charlson co-morbidity index. The following known or suggested risk factors cognitive decline will also be included in the model: baseline cognitive function, education level, type of surgery, preoperative depression, preoperative vascular disease, postoperative complications, composite score on frailty tests and a history of falls. We will use a model with backward elimination, to avoid exclusion of predictors with suppressor effects.

Specific Aim 2: Evaluate whether patients who experience POD have worse quality of life at approximately one year postoperatively.

The primary endpoint of our analysis is quality of life one year after surgery, as measured by the change in VR-12 score between preoperative and postoperative assessments. Again, a multivariable regression analysis will be performed to evaluate whether the development of postoperative delirium is an independent predictor variable for the change in quality of life. The following variables will be included in the model: age, sex, American Society of Anesthesiologists physical score, Charlson co-morbidity index, type of surgery, preoperative depression, preoperative vascular disease, postoperative complications, composite score on frailty tests and a history of falls. As above, we will use a model with backward elimination, to avoid exclusion of predictors with suppressor effects.

For the above aims, we expect this study to be limited by loss to follow-up, estimated to be 50%. Those lost to follow-up are likely to have more severe disease or deterioration in health. In order to determine the influence of missing data in our analysis, we will also conduct a sensitivity analysis. We will calculate the average cognition scores of those who declined. We will repeat the above models including missing subjects, assuming all patients who did not participate had cognitive decline, quantified by the average calculated from participants above.

Specific Aim 3: Explore whether patients who experience POD are more likely to become demented within approximately one to two years of their surgery.

The primary endpoint of our analysis is incident dementia. A Cox proportional hazards regression will be used to explore the likelihood of incident dementia associated with POD. The following variables will be included in the model: age, sex, American Society of Anesthesiologists physical score, Charlson co-morbidity index, preoperative cognitive function, type of surgery, preoperative depression, preoperative vascular disease, postoperative complications, and composite score on frailty tests and a history of falls.

All statistical analyses will be performed using SAS, version 9.4 (SAS Institute, Inc., Cary, North Carolina). To determine whether postoperative delirium increases risk of incident dementia, the Cox proportional hazards model will be one-sided. All other tests will be two-sided. By arbitrary convention all tests will be considered statistically significant at a $p<0.05$, and all results will be presented with estimates and 95% confidence intervals.

11. Pre-specified additional analyses and sub-studies

The primary aim of this study is to determine whether postoperative delirium predicts intermediate-term cognitive impairment. However, as a sub-study of ENGAGES and SATISFY-SOS, several other clinically relevant outcomes can be explored as well. SATISFY-SOS systematically collects detailed information regarding patient centered outcomes, including patient perceived cognition. Correlation between performance on neurocognitive testing and patient perceived cognition would be interesting and useful clinically. Furthermore, the information regarding patients' characteristics will allow exploration of risk factors for intermediate-term cognitive impairment. Lastly, as part of ENGAGES, some patients will have baseline NIH Toolbox cognitive testing, allowing description of long-term cognitive trajectories as evaluated by these tests.

12. Limitations

This study contains several limitations. First, of most concern is the potential for non-response bias if patients who do not participate are not a random subset of those contacted. We will attempt to minimize the non-response rate by offering to visit patients at their homes if patients are unwilling to come to the study center. We expect that those lost to follow-up would be more likely to have more severe disease or health deterioration, potentially affecting cognitive function. We will thus conduct appropriate sensitivity analyses to determine how missing outcomes data could alter the findings of our study. Second, with an observational study, we cannot establish a causal relationship between postoperative delirium and persistent declines in cognitive and quality of life. If an independent relationship is found, we shall not be able to disambiguate whether postoperative delirium in some way causes persistent decline in these outcomes, or whether it is a sign of underlying vulnerability. However, since it is not possible to randomize patients to experience delirium, this limitation might be inevitable. Third, since patients in this study are recruited from a single tertiary care center, the study sample may not be representative of surgical patients in general. While these patients tend to have higher comorbid disease burden then the general surgical population, including comorbidities in the statistical model will account for these differences. Finally, while we have baseline cognitive assessments, we do not have preoperative cognitive trajectories, and thus cannot determine whether the results of cognitive function tests are a deviation from the pre-operative trend.

13. Compliance

13.1 Subject Compliance

The exposure of this study is post-operative delirium, so no monitoring of exposure compliance is necessary. Methods to improve completion of one-year cognitive testing are described in Section 10.3, "Limitations."

13.2 Withdrawal of subjects

Subjects may be withdrawn from the study only if requested by the patient. The reason for withdrawal is recorded by the team's clinical project specialist.

14. Ethical Considerations

This study has been approved by the home institution's Institutional Review Board (IRB ID # 201407128). Written, informed consent is obtained from all participants. As described in Section 7, "Study Groups," no special allowances are made for patients who are blind, deaf, illiterate or not fluent in English. Participants may withdraw from the study at any time.

15. Finance and Insurance

Since this study involves only cognitive testing and surveys, it involves no more than minimal risk to the patients. Finance details, insurance details, and cover for negligent and non-negligent harm are therefore not relevant in this study.

16. Reporting and Dissemination

Results of this study will be published in a scientific journal. Participants will only be notified individually if discoveries are made that directly impact their health.

17. Author Contributions

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. MSA, AA, JZC, MM, RT, TW, EL are responsible for conceptualizing study design. AA, JZC, RT, MM, HM, and AM were responsible for recruitment, enrollment, data collection and editing the protocol. AA, JZC, and RT are responsible for drafting the protocol. All authors including AA, JZC, MM, RT, AM, HM, NL, TW, EL, and MSA have critically revised the protocol and approved the final version.

18. Acknowledgement

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19. Competing Interests

The authors and contributors have no competing interests to disclose.

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22. Table

Type	Variable	Form	Source	Time	Standardized Tool?
Explanatory	Postoperative delirium	Discrete	ENGAGES postoperative assessment	Inpatient postoperative hospital days	Yes
	Charlson Comorbidity Index	Ordinal, 0 to 12	Medical record	Baseline	Yes
	Grip Strength	Continuous	Research team member	Baseline and one year	Yes
	Timed Up and Go	Continuous	Research team member	Baseline and one year	Yes
	History of falls	Dichotomous	Survey	Baseline	N/A
	Postoperative Complications	0, 1, 2, 3+	Survey and medical record	One year	No
	ASA Physical Status	Ordinal, 1 to 6	Anesthesia record	Baseline	Yes
Outcome	Trails A	Continuous	Research team member	Baseline and one year	Yes
	Trails B	Continuous	Research team member	Baseline and one year	Yes
	Stroop Color Word Test	Continuous	Research team member	Baseline and one year	Yes
	Physical quality of life	Continuous	Survey	Baseline and one year	Yes
	Mental Quality of life	Continuous	Survey	Baseline and one year	Yes
	Dementia	Dichotomous	Survey	Baseline and one year	Yes
Confounder	Age	Continuous	Medical record	Baseline	N/A
	Sex	Dichotomous	Medical record	Baseline	N/A
	Education level	< High school, High school, >High school	Research team member	Baseline	N/A
	Functional dependence	Ordinal, 0 to 100	Research team member	Baseline and one year	Yes
	Smoking status	Current, past, never	CPAP assessment	Baseline	N/A
	Depression	Dichotomous	Medical record and survey	Baseline and one year	Yes
	Preoperative vascular disease	Dichotomous	Medical record	Baseline	No
	Type of surgery	Ten categories	CPAP assessment	Baseline	N/A

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page Number
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1 and 3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6-7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7-8
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	7-8
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	9-10
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	9-10
Bias	9	Describe any efforts to address potential sources of bias	11
Study size	10	Explain how the study size was arrived at	9
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	10 and table
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	10
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	10
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	10-11

(*e*) Describe any sensitivity analyses

Continued on next page

Results			**Page Number**
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	N/A
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	N/A
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	N/A
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	N/A
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key results	18	Summarise key results with reference to study objectives	N/A
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	N/A
Generalisability	21	Discuss the generalisability (external validity) of the study results	
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Ability of postoperative delirium to predict intermediate-term postoperative cognitive function in patients undergoing elective surgery at an academic medical center: protocol for a prospective cohort study

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Keywords:	postoperative delirium, postoperative cognitive decline, EEG guidance, quality of life, Dementia < NEUROLOGY, frailty

Title: Ability of postoperative delirium to predict intermediate-term postoperative cognitive function in patients undergoing elective surgery at an academic medical center: protocol for a prospective cohort study

Short title: Postoperative delirium predicting intermediate-term post-operative cognitive function

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Keywords: postoperative delirium, postoperative cognitive decline, EEG guidance, quality of life, dementia, frailty

Abstract

Introduction: Postoperative delirium (POD) is a common complication in elderly patients, characterized by a fluctuating course of altered consciousness, disordered thinking and inattention. Preliminary research has linked POD with persistent cognitive impairment and decreased quality of life. However, these findings maybe confounded by patient co-morbidities, postoperative complications, and frailty. Our objective is to determine whether POD is an independent risk factor for persistent impairments in attention and executive function after elective surgery. Our central hypothesis is that patients with POD are more likely to have declines in cognition and quality of life one year after surgery compared with patients without POD. We aim to clarify whether these associations are independent of potentially confounding factors. We will also explore the association between POD and incident dementia.

Methods and Analysis: This study will recruit 130 patients from the ongoing Electroencephalography Guidance of Anesthesia to Alleviate Geriatric syndromes (ENGAGES) study. Patients who live ≤45 miles from the study center or have a planned visit to the center 10-16 months postoperatively will be eligible. Patients with POD, measured by the Confusion Assessment Method, will be compared to patients without delirium. The primary outcome of cognitive function and secondary outcomes of quality of life and incident dementia will be compared between cohorts. Cognition will be measured by Trails A&B and Stroop Color Word Test, quality of life with Veteran's RAND 12-item Health Survey, and incident dementia with the Short Blessed Test. Multivariable regression analyses and a Cox proportional hazards analysis will be performed. All results will be reported with 95% confidence intervals and α=0.05.

Ethics and Dissemination: The study has been approved by the Washington University in St. Louis Institutional Review Board (IRB #201601099). Plans for dissemination include scientific publications and presentations at scientific conferences.

Trial registration: This is a pre-specified sub-study of ENGAGES (NCT02241655).

Strengths and Limitations of this study:

Strengths:

- Postoperative intermediate term cognitive function and quality of life are important patient-centered outcomes.
- Analysis will include salient patient characteristics, including preoperative cognition, comorbid conditions and frailty.
- Study sample will consist of an understudied population in clinical research.

Limitations:

- Potential for loss to follow-up and non-response bias
- Since this is an observational study, we cannot establish a causal relationship between postoperative delirium and persistent declines in cognition and quality of life.
- We cannot determine whether cognitive function deviates from the pre-operative trend, without multiple preoperative cognitive assessments to establish a trajectory.

Background

Since Bedford's 1955 case series suggesting an association between surgical intervention and cognitive impairment, there has been growing concern among the public that cognitive decline is a common consequence of surgery.[1] This pervasive view continues to concern patients and their families, fueled by anecdotal evidence and media coverage. Postoperative cognitive decline (POCD) has been a growing topic for scientific investigation after several studies were published by the International Study of Post-Operative Cognitive Dysfunction (ISPOCD) group. While several influential studies demonstrated early postoperative cognitive decline (POCD) lasting up to 3 months, the persistence of this cognitive decline has been controversial.[2-6] Importantly, the population of Americans older than 60 years is projected to double over the next 30 years,[7] and many will require surgery. Acute and long-term cognitive changes related to surgical intervention are particularly distressing to patients and their families. Therefore, clarification of cognitive outcomes would assist patients and practitioners in making an informed decision about the relative risks and benefits of proceeding with elective surgery.

Literature search and review

A systemized literature review was conducted with the help of a librarian experienced in systemic review (see Acknowledgement). Ovid Medline was searched for studies published between 1981 and September 2016 using the query: Postoperative or after surgery AND Delirium AND Cognitive function or dementia AND Elderly AND Long-term or intermediate term or follow up or cohort studies or retrospective studies. Articles in English or with English translation were considered. JC and RT reviewed the 301 search results and found 28 articles that were relevant to our clinical question. 21 out of the 28 relevant articles (75%) showed significant result in the relationship between postoperative delirium

(POD) and intermediate- to long-term cognitive decline (Appendix A). These seem to suggest a high pre-test probability in studying the ability of POD to predict intermediate-term cognitive decline. However, these studies are heterogeneous in the study design, selected surgical patient population, and outcome measurement tools complicating synthesis of the systemic search to draw conclusions.

POD is a common complication for surgical patients over the age of 60 years.[8] It is a neurological syndrome characterized by a combination of features, which must include an acute change, fluctuating course, inattention, and may also include disordered thinking or altered consciousness. Although usually transient, POD has been associated with several salient adverse outcomes, including mortality, prolonged ICU stay and persistent cognitive decline.[9-12] One prospective cohort study of cardiac surgery patients suggested patients experiencing POD had prolonged cognitive impairment at one year, and those with longer duration of delirium had slower recovery.[12] However, after adjusting for baseline differences in cognitive function, there was no significant difference compared with controls. The same study also demonstrated that mild cognitive impairment preoperatively may predispose patients to delirium; thus POD may be exposing patients who are already experiencing sub-clinical cognitive decline or those who have an underlying vulnerability to cognitive decline. Another study, in orthopedic surgery patients found no association between POD and cognitive decline at three months.[13] While several studies have suggested that postoperative cognitive decline can persist past six months after surgery,[2, 14] others have demonstrated a transient early decline with later recovery.[4, 5] Furthermore, there is conflicting evidence regarding the long-term cognitive trajectories of postoperative patients, with some suggesting overall improvement and others suggesting overall decline.[15, 16] POD has been posited as a risk factor for lasting decline; however, few articles have addressed the association between POD and persistent postoperative cognitive decline (arbitrarily defined as lasting >6 months). A prospective matched controlled survey with an average of 30-month follow-up demonstrated that dementia or mild cognitive impairment was diagnosed in 77.8% of the surviving hip surgery patients with POD, almost doubling the 40.9% rate of control patients (relative risk = 1.9, 95% CI = 1.1-3.3). However the study was underpowered to evaluate the long-term cognitive function, as the power calculation was based on the original study and no intermediate assessments were made to track patients' cognitive function.[17] Another prospective cohort study followed patients over 36 months and found that patients with POD initially had cognitive decline with a transient recovery, but then exhibited an accelerated pace of long-term cognitive decline when compared to controls.[18] Overall, the results of these studies suggest an association between POD and persistent cognitive impairment, however compelling data supporting an independent association are lacking. Many of these studies also do not consider the duration of delirium, which may portend long-term cognitive decline.[19, 20]

Pre-existing dementia or cognitive impairment is a known risk factor for POD,[8] and several studies suggest an association between POD and dementia. One study in elderly orthopedic surgery patients reported a relative risk of dementia in patient with POD of 10.5 compared to those without POD.[21] A recent study demonstrated a similar association in elderly cardiac surgery patients.[22] However it remains unclear whether POD causes, accelerates, or signifies an underlying vulnerability to cognitive impairment, thus further investigation is warranted.

In addition to cognitive outcomes, quality of life and functional capacity are also important patient-centered outcomes that require further investigation. While one study found that elderly surgical patients tended to have long-term cognitive and functional decline compared to non-surgical patients,[23] few studies have examined the association between cognitive function and quality of life or activities of daily living. One prospective study over a 10-month period demonstrated that delirium was an independent risk factor for becoming dependent for personal activities of daily living after ICU

discharge (OR = 2.188, P <0.046) and that patients with POD also demonstrated a greater decline in Short-Form-36 domains after discharge, especially in physical function, vitality, and social function.[24] However, this study could not draw conclusions regarding cognitive function due to lack of data. Kastaun et al. reported perceived impairment in ability to perform activities of daily living one year after surgery, however did not detect significant cognitive decline at that time.[25] It remains unclear whether cognitive decline results in impaired functional capacity or decreased quality of life. In fact, given the variable definitions of POCD, data from previous studies are difficult to interpret. As many of the deficits found in neuropsychiatric testing are subtle, it is possible that detected cognitive impairment has no clinically significant impact on these patient-centered outcomes. Instead of using an arbitrary threshold to dichotomize cognitive function as normal or impaired, it would be more informative to correlate these outcomes with cognitive function as a continuous variable or stratified into multiple groups.

At our institution, patient reported postoperative outcomes are gathered as part of the Systematic Assessment and Targeted Improvement of Services Following Yearlong Surgical Outcomes Surveys (SATISFY-SOS) initiative (NCT02032030). Additionally, the ongoing randomized controlled trial: Electroencephalography (EEG) Guidance of Anesthesia to Alleviate Geriatric syndromes (ENGAGES) study, is evaluating patients for postoperative delirium.[26] Using the scaffold provided by these studies, we aim to identify whether delirium is an independent predictor for intermediate-term cognitive function and quality of life.

Justification

The population of older adults is projected to double over the next thirty years, and many will undergo elective surgery with the hope of overall improvement in health and quality of life. Postoperative delirium is a common and potentially preventable complication, thus clarification of its association with persistent declines in cognition and quality of life will inform perioperative care. Prior studies have not demonstrated an association independent of pre-existing patient characteristics and perioperative course. The proposed study addresses the methodologic concerns in current literature by: 1. objectively evaluating attention and executive function with validated cognitive tests, 2. obtaining measurements of baseline cognitive function, 3. conducting statistical analysis which includes important potential confounding factors including frailty measures, and 4. sampling from an unselected surgical population. Given that delirium is predominantly a disorder of attention and executive function, we will focus our investigation on these cognitive domains. The results of this study will contribute to the broader understanding of postoperative cognitive changes, and may help identify and provide therapies for susceptible patients earlier to ultimately improve outcomes.

As part of the ENGAGES study, patients have been enrolling since January 2015, with 804 patients enrolled thus far. Over the last year, the ENGAGES research team has enrolled approximately 35 patients per month, and has gathered baseline cognitive data on a majority of participants. Preliminary screening suggests about 65% of those enrolled in ENGAGES are eligible for the current study. Anticipating that half of those contacted will enroll, we expect to assess 10 to 15 patients per month. The scaffold of ENGAGES and trained study members make this sub-study highly feasible.

Specific Aims

Specific Aim #1: Determine whether the incidence and duration of postoperative delirium predict worse performance on specific cognitive tests at approximately one year after surgery.

We hypothesize that postoperative delirium is independently associated with poorer performance on tests of attention and executive function at one year after surgery, and that patients with a longer duration of delirium will have more marked cognitive decrement. We will conduct a regression analysis, including likely contributory variables, to assess the association between delirium and cognitive decline at approximately one year.

Specific Aim #2: Evaluate whether the incidence and duration of postoperative delirium predict worse quality of life at approximately one year postoperatively.

We hypothesize that postoperative delirium is independently associated with decreased quality of life one year after surgery, and that patients with a longer duration of delirium will have more marked decrease in health-related quality of life. We will conduct a regression analysis, including likely contributory variables, to assess the association between delirium and health-related quality of life at approximately one year.

Specific Aim #3: Explore whether patients who experience postoperative delirium are more likely to develop dementia within approximately one to two years of their surgery.

We hypothesize that postoperative delirium is independently associated with incident dementia one to two years after surgery. We will conduct a Cox proportional hazards regression, including likely contributory variables, to assess the rate of incident dementia approximately one to two years after surgery.

Study Design:

This prospective cohort study is pre-specified sub-study of the ENGAGES study. The ENGAGES study is a randomized clinical trial enrolling approximately 1,200 patients sixty years and older who will undergo elective major surgery at Barnes Jewish Hospital (BJH), St. Louis, MO.

The parent trial will recruit patients primarily from the Center for Preoperative Assessment and Planning (CPAP) clinic. Among inclusion criteria for ENGAGES, details of which have been previously published,[26] is enrollment in the SATISFY-SOS study.[27] As part of ENGAGES, participants will complete a comprehensive baseline assessment including cognitive tests, frailty measures, and screening for delirium and dementia. Postoperatively, patients will have daily evaluations for delirium during the hospital stay. The current study will retrospectively identify 130 participants who reside within approximately 45 miles from the hospital or those who have a planned visit to the hospital between ten to sixteen months post-operatively. Patients diagnosed with delirium postoperatively will be compared to those without delirium. A prospective intermediate-term postoperative assessment will be conducted by a research team member blinded to whether the patient developed postoperative delirium.

Study Groups

The target population for this study is patients who underwent preoperative assessment for elective surgery at the Center for Preoperative Assessment and Planning (CPAP) clinic at Barnes Jewish Hospital (BJC) in St. Louis, Missouri. The ENGAGES study is enrolling 1,232 patients who are already enrolled in the STATISFY-SOS study. Inclusion criteria include patients sixty 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 two days postoperatively (i.e., 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). The ENGAGES study has minimal exclusion, as there are no absolute contraindications to EEG monitoring. Exclusion criteria include neurosurgical procedures, preoperative delirium, patients who are unable to participate adequately in delirium screening, including those who are blind, deaf, illiterate, or not fluent in English, patients with a history of intraoperative awareness during intended general anesthesia, and patients who had a second surgery planned within five days after the index surgery. This prospective study will enroll 130 patients who are already enrolled in the ENGAGES and SATISFY-SOS studies (Appendix B). In addition to previously described inclusion and exclusion criteria, participants will be included in this study if their home residence is ≤45 miles from BJH or they have a planned visit to the hospital within the specified timeframe. Patients who have not completed the baseline cognitive assessment with Trails A, Trails B and the Stroop Color Word Test will also be excluded from this study.

Recruitment

As part of the SATISFY-SOS study, patients have given informed consent to be contacted by Washington University for follow-up of health-related outcomes up to a year after surgery. Eligible participants will be identified by chart review and query of the ENGAGES REDCap database. A member of the research team will contact potential participants by telephone approximately ten to sixteen months after surgery for enrollment in this study. Patients may refuse participation in the study. If patients agree to participation, written consent will be obtained when the patient comes in for assessment, prior to any data collection. Patients will then be prospectively evaluated with assessments of cognition, quality of life, and frailty measures, which are described in detail below. Meal vouchers will be provided for participation. Patients residing within approximately 45 miles of the hospital, who are willing to participate in the study, but unable or unwilling to come to the study center will be offered assessment at home by a member of the research team. Additionally, ENGAGES patients who have not completed a one-year dementia screening will be contacted by telephone approximately 18 to 24 months after surgery. Phone consent will be obtained to complete dementia screening over the telephone. Participants may refuse to participate.

Data

Data Collection

Routinely obtained baseline assessment in the CPAP clinic includes demographic information, a detailed medical history, surgical history, medications and physical examination. As part of SATISFY-SOS and ENGAGES, baseline assessment using the Barthel Index, Veteran's RAND 12-item Health Survey (VR-12), Eight-item Interview to Differentiate Aging and Dementia (AD-8), Short Blessed Test (SBT), alcohol sniff test, and Personal Health Questionnaire Depression Scale (PHQ8) will be performed. Baseline cognitive function will be evaluated by the ENGAGES team with the Trails A and B, and the Stroop Color and Word Test. Some patients may complete computer-based cognitive testing with the NIH toolbox at baseline (described below). Additionally, frailty will be assessed using grip strength, Timed-up and Go (TUG) test, and obtaining fall history at baseline. Participants will have daily delirium assessments by trained

researchers with the Confusion Assessment Method in the postoperative period for the duration of their hospital stay. Data collected by the ENGAGES team will be entered into the Washington University School of Medicine Research Electronic Data Capture (REDCap) application. [18] Perioperative data will be retrieved from the hospital's perioperative electronic medical record (Metavision by iMDsoft®, Needham, MA). High fidelity perioperative data is routinely captured from our EMR to an SQL server (Microsoft, Redmond, WA) database. These data include bispectral index (BIS) values, EEG burst suppression durations, laboratory data, intraoperative medications, physiological readings, and postoperative recovery parameters. 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.

Cognition: The primary outcome in this study will be a composite score comprised of scores from three cognitive tests evaluating attention and executive function: Trails A, Trails B and Stroop Color Word Test. These cognitive tests will be repeated approximately one year after surgery to evaluate intermediate term cognitive function. The research team member performing the assessments will be blinded to whether the patient developed postoperative delirium. In addition to the above tests, this study proposes to use the Cognition Battery of the National Institutes of Health (NIH) Toolbox Assessment of Neurological and Behavioral Function (http://www.nihtoolbox.org). The NIH Toolbox Cognition Battery (Feinberg School of Medicine, Northwestern University, Chicago, IL), is a comprehensive yet concise standardized computer-based assessment battery; we plan to include tasks to evaluate attention (Flanker Inhibitory Control and Attention Test), episodic memory (Picture Sequence Memory Test),and executive function (Dimensional Change Card Sort Test and Flanker Inhibitory Control and Attention Test). Patients will complete the NIH Toolbox Cognition tests above, which takes approximately 10 minutes to complete. The NIH Toolbox Cognition Battery has been validated for use across a wide range of ages.[28, 29] Self-reported cognitive function will be evaluated by The Patient Reported Outcomes Measurement Information System (PROMIS). PROMIS, funded by the National Institutes of Health (NIH), is a set of highly reliable, valid, flexible, precise, and responsive assessment tools that measure patient–reported health status. PROMIS v1.0-Applied Cognition-General Concerns-Short Form 4a is comprised of four questions about thinking and cognition. PROMIS v1.0-Applied Cognition-Abilities-Short Form 4a is comprised of four questions about memory. Evaluation for dementia with the SBT will be completed for all patients at baseline, and again between one to two years after surgery. The SBT has been shown to have 95% sensitivity for detecting cognitive dysfunction when compared with the MMSE, and can be administered in approximately 3 minutes, making it an excellent screening tool.[30]

Quality of Life: As part of the ongoing SATISFY-SOS study, patient self-reported Health-related Quality of Life information will be assessed through the VR-12 at baseline (preoperatively) and also one year after surgery. The VR-12 was derived from the Veterans RAND 36 Item Health Survey (VR-36) and contains twelve 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.[31]

Functional status: We will assess functional status with the Barthel Index for Activities of Daily Living and Lawton Instrumental Activities of Daily Living Scale. The Barthel Index is a measure of patient performance in ten activities comprised of eight questions about personal care and two questions about mobility. The Lawton Scale assesses independent living skills in 8 areas of function.

Frailty: We will measure grip strength and the Timed Up and Go (TUG) test. Grip strength will also be assessed with three measurements in the dominant hand using a Jamar® handheld dynamometer (Lafayette Instruments, Lafayette, IN). Maximal grip strength will be selected for analysis.

Data management

A customized database has been developed to facilitate data management for this study using the Research Electronic Data Capture (REDCap) system. REDCap is a secure web-based data capture system available to research groups receiving support from the Institute of Clinical and Translational Sciences at Washington University. It is maintained by the Washington University Division of Biostatistics with multiple capabilities to simplify data management and analysis. These include intuitive data entry, data audit and tracking, import of externally sourced data, and automated data export for analysis. REDCap requires unique user identification and password combinations for secure access.

Statistical Consideration

Sample calculations

For specific aims 1&2, sample size calculations have been performed using G*POWER 3.0.10. Power analysis for a multiple regression with 15 predictors was conducted to determine a sufficient sample size using an alpha of 0.05, a power of 0.9, and a medium effect size ($f^2 = 0.1$). Based on the aforementioned assumptions, the desired sample size is 130 patients. Assuming 10% of participants consented may withdraw from the study, we will recruit 143 patients.

For specific aim 3, sample size calculation has been performed using PS 3.1.2. 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 POD of 25%. A previous study has reported the median age at the onset of dementia to be approximately 84 years old.[32] To detect a hazard ratio of 2.0 in patients with delirium compared to those without delirium, with 80% power and α=0.05, we will need 516 patients (129 in the delirium goup, and 387 in the control group). To account for a 10% attrition rate, we will recruit 570 patients.

Statistical analysis

We will perform and report descriptive statistics (mean and standard deviation) for all variables between patients with and without the diagnosis of POD. Descriptive statistics will include chi-squared tests for categorical variables, t-tests for normally distributed continuous variables and Mann-Whitney tests for nonparametric continuous variables.

Specific Aim 1: Determine whether patients who experience POD perform worse on specific cognitive tests at approximately one year after surgery.

The primary endpoint of our analysis is cognitive function one year after surgery, as measured by the Trails A &B and the Stroop Color Word Test. Z-scores will be calculated for performance for each test, and combined to form a composite measure. Multivariable regression analysis will be used to determine whether the development of postoperative delirium is a predictor variable for cognitive function, independent from other possible contributory factors. POD will be entered as two categorical variables: for incidence (present or absent) and for duration (<3 days POD or ≥3 days POD). The following

variables will be included in the model: age, sex, American Society of Anesthesiologists physical score, and Charlson co-morbidity index. The following known or suggested risk factors cognitive decline will also be included in the model: baseline cognitive function, education level, type of surgery, randomization group, preoperative depression, preoperative vascular disease, postoperative complications, composite score on frailty tests and a history of falls. We will use a model with backward elimination, to avoid exclusion of predictors with suppressor effects. While cognition will be entered as a continuous variable, we will consider a change of one standard deviation in cognitive score as a minimal clinically important difference.

Specific Aim 2: Evaluate whether patients who experience POD have worse quality of life at approximately one year postoperatively.

The primary endpoint of our analysis is quality of life one year after surgery, as measured by the change in VR-12 score between preoperative and postoperative assessments. Again, a multivariable regression analysis will be performed to evaluate whether the development of postoperative delirium is an independent predictor variable for the change in quality of life. POD will be entered as two categorical variables: for incidence (present or absent) and for duration (<3 days POD or ≥3 days POD). The following variables will be included in the model: age, sex, American Society of Anesthesiologists physical score, Charlson co-morbidity index, type of surgery, randomization group, preoperative depression, preoperative vascular disease, postoperative complications, cognitive function, composite score on frailty tests and a history of falls. As above, we will use a model with backward elimination, to avoid exclusion of predictors with suppressor effects. Previous work by our group has calculated the minimal clinically important difference for overall VR-12 quality of life to be 1.4 for improvement and 3.6 for deterioration.[33]

For the above aims, we expect this study to be limited by loss to follow-up, estimated to be 50%. Those lost to follow-up are likely to have more severe disease or deterioration in health. In order to determine the influence of missing data in our analysis, we will also conduct a sensitivity analysis. We will calculate the average cognition scores of those who declined. We will repeat the above models including missing subjects, assuming all patients who did not participate had cognitive decline, quantified by the average calculated from participants above. Additionally, to examine whether our sample selection method may bias the results, we will compare baseline characteristics of those ENGAGES patients who were eligible for our study to those who were not eligible.

Specific Aim 3: Explore whether patients who experience POD are more likely to become demented within approximately one to two years of their surgery.

The primary endpoint of our analysis is incident dementia. A Cox proportional hazards regression will be used to explore the likelihood of incident dementia associated with POD. POD will be entered as a dichotomous variable (absent or present). The following variables will be included in the model: age, sex, American Society of Anesthesiologists physical score, Charlson co-morbidity index, preoperative cognitive function, type of surgery, randomization group, preoperative depression, preoperative vascular disease, postoperative complications, and composite score on frailty tests and a history of falls.

All statistical analyses will be performed using SAS, version 9.4 (SAS Institute, Inc., Cary, North Carolina). All other tests will be two-sided. By arbitrary convention all tests will be two-sided and considered statistically significant at a $p<0.05$, and all results will be presented with estimates and 95% confidence intervals.

Pre-specified additional analyses and sub-studies

The primary aim of this study is to determine whether postoperative delirium predicts intermediate-term cognitive impairment. However, as a sub-study of ENGAGES and SATISFY-SOS, several other clinically relevant outcomes can be explored as well. SATISFY-SOS systematically collects detailed information regarding patient centered outcomes, including patient perceived cognition. Correlation between performance on neurocognitive testing and patient perceived cognition would be interesting and useful clinically. Furthermore, the information regarding patients' characteristics will allow exploration of risk factors for intermediate-term cognitive impairment. To investigate effects on memory, we will perform a secondary analysis comparing the results of the SBT. Lastly, as part of ENGAGES, some patients will have baseline NIH Toolbox cognitive testing, allowing description of long-term cognitive trajectories as evaluated by these tests.

Limitations

This study contains several limitations. First, of most concern is the potential for non-response bias if patients who do not participate are not a random subset of those contacted. We will attempt to minimize the non-response rate by offering to visit patients at their homes if patients are unwilling to come to the study center. We expect that those lost to follow-up would be more likely to have more severe disease or health deterioration, potentially affecting cognitive function. We will thus conduct appropriate sensitivity analyses to determine how missing outcomes data could alter the findings of our study. Second, with an observational study, we cannot establish a causal relationship between postoperative delirium and persistent declines in cognitive and quality of life. If an independent relationship is found, we shall not be able to disambiguate whether postoperative delirium in some way causes persistent decline in these outcomes, or whether it is a sign of underlying vulnerability. However, since it is not possible to randomize patients to experience delirium, this limitation might be inevitable. Third, since patients in this study are recruited from a single tertiary care center, the study sample may not be representative of surgical patients in general. While these patients tend to have higher comorbid disease burden then the general surgical population, including comorbidities in the statistical model will account for these differences. Finally, while we have baseline cognitive assessments, we do not have preoperative cognitive trajectories, and thus cannot determine whether the results of cognitive function tests are a deviation from the pre-operative trend.

Compliance

Subject Compliance

The exposure of this study is post-operative delirium, so no monitoring of exposure compliance is necessary. Methods to improve completion of one-year cognitive testing are described in Section 10.3, "Limitations."

Withdrawal of subjects

Subjects may be withdrawn from the study only if requested by the patient. The reason for withdrawal is recorded by the team's clinical project specialist.

Ethical Considerations

This study has been approved by the home institution's Institutional Review Board (IRB ID # 201407128). Written, informed consent is obtained from all participants. As described in Section 7, "Study Groups," no special allowances are made for patients who are blind, deaf, illiterate or not fluent in English. Participants may withdraw from the study at any time.

Finance and Insurance

Since this study involves only cognitive testing and surveys, it involves no more than minimal risk to the patients. Finance details, insurance details, and cover for negligent and non-negligent harm are therefore not relevant in this study.

Reporting and Dissemination

Results of this study will be published in a scientific journal. Participants will only be notified individually if discoveries are made that directly impact their health.

Author Contributions

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. MSA, AA, JZC, MM, RT, TW, EL are responsible for conceptualizing study design. AA, JZC, RT, MM, HM, and AM were responsible for recruitment, enrollment, data collection and editing the protocol. AA, JZC, and RT are responsible for drafting the protocol. All authors including AA, JZC, MM, RT, AM, HM, NL, TW, EL, and MSA have critically revised the protocol and approved the final version.

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Competing Interests

The authors and contributors have no competing interests to disclose.

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Table

Type	Variable	Form	Source	Time	Standardized Tool?
Explanatory	Postoperative delirium incidence	Dichotomous (present or absent)	ENGAGES postoperative assessment	Inpatient postoperative hospital days	Yes
	Postoperative delirium duration	Categorical (<3 days or ≥3 days)	ENGAGES postoperative assessment	Inpatient postoperative hospital days	N/A
	Charlson Comorbidity Index	Ordinal, 0 to 12	Medical record	Baseline	Yes
	Grip Strength	Continuous	Research team member	Baseline and one year	Yes
	Timed Up and Go	Continuous	Research team member	Baseline and one year	Yes
	History of falls	Dichotomous	Survey	Baseline	N/A
	Postoperative Complications	0, 1, 2, 3+	Survey and medical record	One year	No
	ASA Physical Status	Ordinal, 1 to 6	Anesthesia record	Baseline	Yes
Outcome	Trails A	Continuous	Research team member	Baseline and one year	Yes
	Trails B	Continuous	Research team member	Baseline and one year	Yes
	Stroop Color Word Test	Continuous	Research team member	Baseline and one year	Yes
	Physical quality of life	Continuous	Survey	Baseline and one year	Yes
	Mental Quality of life	Continuous	Survey	Baseline and one year	Yes
	Dementia	Dichotomous	Survey	Baseline and one year	Yes
Confounder	Age	Continuous	Medical record	Baseline	N/A
	Sex	Dichotomous	Medical record	Baseline	N/A
	Education level	< High school, High school, >High school	Research team member	Baseline	N/A
	Functional dependence	Ordinal, 0 to 100	Research team member	Baseline and one year	Yes
	Smoking status	Current, past, never	CPAP assessment	Baseline	N/A
	Depression	Dichotomous	Medical record and survey	Baseline and one year	Yes
	Preoperative	Dichotomous	Medical record	Baseline	No

	vascular disease				
	Type of surgery	Ten categories	CPAP assessment	Baseline	N/A
	ENGAGES randomization	Dichotomous	Research team member	Day of surgery	N/A

Appendix A.

Protocol Literature Review

Author	Study Design	Sample size	Patient Pop.	Outcomes	Assessment	Follow-up	Results
Tow et al[1]	Prospective cohort	142	Older adults undergoing elective orthopedic surgery	Incidence and severity of POD	CAM, Memorial Delirium Assessment Scale, cognitive reserve (literacy and cognitive activities)	First assessment median 22 hrs postoperatively, second assessment median 32 hrs postoperatively	Greater participation in cognitive activity was associated with lower incidence and severity of delirium
Neufeld et al[2]	Prospective cohort	91	Consecutive patients undergoing surgical procedure, ≥ 70 y/o	Cognitive functioning	ADLs, IADLs, MMSE, Word Fluency, Digit Span, DSM-IV delirium criteria	19 months postoperatively	No differences in any outcomes between patients with versus without PACU delirium
Sprung et al[3]	Population based prospective cohort	1,731	70-89 y/o (data abstracted retrospectively for anesthesia exposure from 40 years old until time of evaluation)	Mild cognitive impairment	1) impairment in one of the four cognitive domains; 2) cognitive concerns by the subject, informant, examining nurse, or physician; 3) essentially normal functional activities, and; 4) absence of dementia (based on published criteria)	Median 4.8 years	31% developed MCI; Cumulative exposure to procedures requiring GA after the age 40 was not associated with the development of incident MCI in cognitively normal elderly participants. Does not exclude possibility that anesthetic exposures occurring later in life may be associated an increase in the rate of incident MCI, especially in patients undergoing vascular surgery
Hempenius et al[4]	RCT	260	Consecutive patients ≥65 years undergoing surgery for a solid tumor	mortality, rehospitalization, ADL functioning, return to the independent pre-operative living situation, use of supportive care, cognitive functioning and health related QOL	DOS for delirium, MMSE for cognition	3 months	Geriatric liaison intervention did not improve outcomes. POD was associated with: an increased risk of decline in ADL functioning, an increased use of supportive assistance, and a decreased chance to return to the independent preoperative living situation.
Youngblom et al[5]	Prospective cohort	421	>65 y/o, noncardiac surgery	Delirium and POCD	For delirium: CAM; for POCD: verbal fluency, digit	2 days postop	80% of patients experienced delirium or POCD on POD1. 48%

					symbol test, and word list		experienced postoperative delirium on POD1, POD2, or both days. The delirium group had a lower preoperative cognitive status score. incidence of pre-existent dementia was not different between the group that developed delirium and the group that did not.
Hussain et al[6]	Review	N/A	N/A	Relationship between general anesthesia, major surgery, and dementia, specifically AD	N/A	N/A	Future studies need: sufficient sample size, good control group (no anesthesia, no surgery, well-matched otherwise), preop cognitive assessment, maybe use biomarkers for AD.
Abelha et al[7]	Prospective	562	SICU patients	Primary: Mortality Secondary: hospital mortality and "becoming dependent"	ICDSC for postoperative delirium, SF-36 for health-related QOL	6 months	POD is an independent risk factor for mortality, hospital mortality, and becoming dependent for personal ADLs. Delirium incidence: 16%
Witlox et al[8]	Prospective cohort nested w/in RCT	53	≥75 years old, hip fracture repair	Delirium and postoperative cognitive decline	Delirium: CAM Cognition: MMSE, the expanded digit span test, and the GDS	3 months	All pts who developed delirium were asked to f/u and an equal number of control pts invited to f/u as well; 5 patients still delirious at 3 months; delirium was associated with impairments in global cognition and episodic memory at follow-up
Radtke et al[9]	RCT	1155	≥60 y/o with at least 60 minute surgery with general anesthesia	Delirium and postoperative cognitive dysfunction	Delirium: DSM IV delirium criteria Cognition: Motor Screening Test, two tests of visual memory and a test of attention, visual verbal learning test and the Stroop Color Word interference test	Assessed for delirium while admitted, f/u at 1 week and 3 months	Delirium incidence was lower in the BIS-monitored group (16.7 vs 21.4%), but POCD was not different in the BIS vs non-BIS group.
Saczynski et al[10]	Prospective cohort	225	>60 y/o, undergoing CABG or	Delirium and cognition	Delirium: CAM; Cognition: MMSE	Delirium assessed starting POD2	Delirium incidence: 43%; Those who developed delirium has a lower

			valve replacement			until pt discharge; Cognitive tests preop and at 1, 6, and 12 months postop	preoperative cognitive score.
Koster et al[11]	Prospective follow-up study	300	>45 y/o undergoing elective cardiac surgery	Delirium, postoperative cognition and functionality, Mortality, readmission	Delirium: DOS scale; Cognition: SF-36, the Cognitive Failure Questionnaire, and a purpose-designed questionnaire	6 months	Delirium incidence: 17%; Delirium was associated w/increased mortality, a higher hospital readmission rate, lower quality of life, cognitive failure, and reduced mobility.
Quinlan et al[12]	Secondary analysis of prospective study	1218 (948 completed 3 month functional assessment)	Non-cardiac surgery, ≥ 60 y/o	Delirium, cognition, POCD	MMSE, chart review, ISPOCD neuropsychological tests	3 months postoperatively	After adjustment for age, sex, education, cognition, and surgery duration, delirium remained associated with functional decline
Wallbridge et al[13]	Prospective cohort	89	Patients undergoing elective abdominal aortic aneurysm surgery y/o	Cognition and function	Battery of cognitive measures, Portland Adaptability Inventory (PAI) for function	3 months postoperatively	Cognitive impairment postoperatively was mild but was associated with number of days delirious and preoperative deficits in verbal memory and psychomotor speed
Jankowski et al[14]	Prospective cohort	418	≥ 65 y/o, undergoing total hip or knee arthroplasty	Delirium, cognition, function	CAM, MMSE, neurocognition and functional testing (American National Adult Reading Test, AVLT, COWAT, SCWT, CAGE, IADL)	3 months postoperatively	Independent predictors of POD included age, history of psychiatric illness, decreased functional status, and decreased verbal memory
Rudolph et al[15]	Prospective cohort	190	≥ 60 y/o, elective or urgent cardiac surgery	Delirium, activities of daily living (function)	CAM, IADL	1 and 12 months postoperatively	Delirium associated with functional decline at 1 month and tended toward association at 12 months
Koster et al[16]	Prospective cohort	112	Consecutive patients undergoing elective cardiac surgery, ≥ 45 y/o	Delirium, mortality, readmission, cognition, function	DSM-IV criteria, study designed questionnaire for cognition	1-1.5 years after surgery	POD associated with increased mortality, readmission, memory and concentration problems, and sleep disturbance

Gogol et al[17]	Review	N/A	N/A	Cognition, dementia, mortality, functional status	N/A	N/A	Delirium is associated with increased short- and long-term mortality, iatrogenic complications, functional decline, and future development of cognitive impairment or dementia.
Bickel et al[18]	Prospective cohort	200	Consecutive hip surgery patients ≥ 60 years old	Delirium, cognition, mortality, need for long term care	MMSE, CAM	8 to 38 months postoperatively	Delirium was a strong independent predictor of cognitive impairment and severe dependency in activities of daily living - more marked long- than for the short-term
Kat et al[19]	Prospective matched controlled cohort	112	Hip surgery patients ≥70 y/o	Delirium, dementia/mild cognitive impairment (MCI)	CAM, MMSE	30 months postoperatively	Delirium associated with increased risk of dementia/MCI, mortality, and institutionalization
Rudolph et al[20]	Prospective cohort	1218	Non-cardiac surgery, ≥ 60 y/o	Delirium, cognition, POCD	MMSE, chart review, ISPOCD neuropsychological tests	7 days and 3 months postoperatively	Delirium associated with early but not late POCD
Olofsson et al[21]	Prospective cohort	61	Consecutive patients undergoing femoral head fracture operation, ≥ 70 y/o	Delirium, LOS, activities of daily living	IADL, Cognition: MMSE, Delirium: OBS, Depression: GDS-15, PGCMS, S-COVS	4 months postoperatively	Delirium incidence: 68%. Delirium was associated with more dementia and depression before their fractures, longer LOS after surgery, and more dependence before surgery, on discharge, and at 4 month f/u.
Rothenhausler et al[22]	Prospective cohort	30	Patients undergoing cardiac surgery with CPB	Cognition, depression, posttraumatic stress symptoms, health status, delirium	Syndrom Kurztest, SF-36, Delirium Rating Scale (DRS)	1 year postoperatively	Lower cognition associated with lower HRQOL
Duppils et al[23]	Prospective cohort	115	≥ 65 y/o, prior participation in observational hip fracture - delirium study	Delirium, cognition, quality of life	DMS-IV criteria for delirium, MMSE, SF-36	6 months postoperatively	Delirium associated w/ greater cognitive deterioration in hospital, lower health-related quality of life at follow up
Edelstein et al[24]	Prospective cohort	921	≥ 65 y/o, operatively treated hip fracture	Postoperative complication rates, in-hospital		1 year follow up	POD incidence: 5.1%. Patients w/ POD had longer LOS, higher 1 year mortality, less likely to

				mortality, hospital LOS, hospital discharge status, 1-year mortality rate, place of residence, recovery of ambulatory ability, and activities of daily living			recover level of ambulation, more likely to show a decline independence. No difference in postoperative complications, in-hospital mortality, discharge residence, and recovery of instrumental activities of daily living at 1 year.
Adunsky et al[25]	Retrospective cohort	281	Elderly hip fracture patients	Cognition, delirium, function	MMSE, CAM, functional independence measure (FIM)	1 week postop and at discharge	Delirium patients tend to be more disabled and more cognitively impaired
Lundstrom et al[26]	Prospective cohort	78	≥ 65 y/o, non-demented, femoral neck fracture	Dementia and mortality	Organic Brain Syndrome (OBS) scale and MMSE	5 year follow up	Increased dementia and mortality in patients with POD vs. not
Edlund et al[27]	Prospective cohort	54	Consecutive patients admitted for femoral neck fractures, age range 40-98 y/o	Postoperative delirium incidence	OBS	6 months follow up	POD incidence: 27.8%. Dementia & increased surgery wait time = greater POD incidence; delirium = worse outcomes after surgery
Goldstein et al[28]	Prospective cohort	362	General surgical, orthopedic, non-surgical, ≥ 55 y/o	Postoperative decline	Psychosocial questionnaire, tests of cognition, affect, function	10 months postoperatively	No significant contribution to changes from baseline

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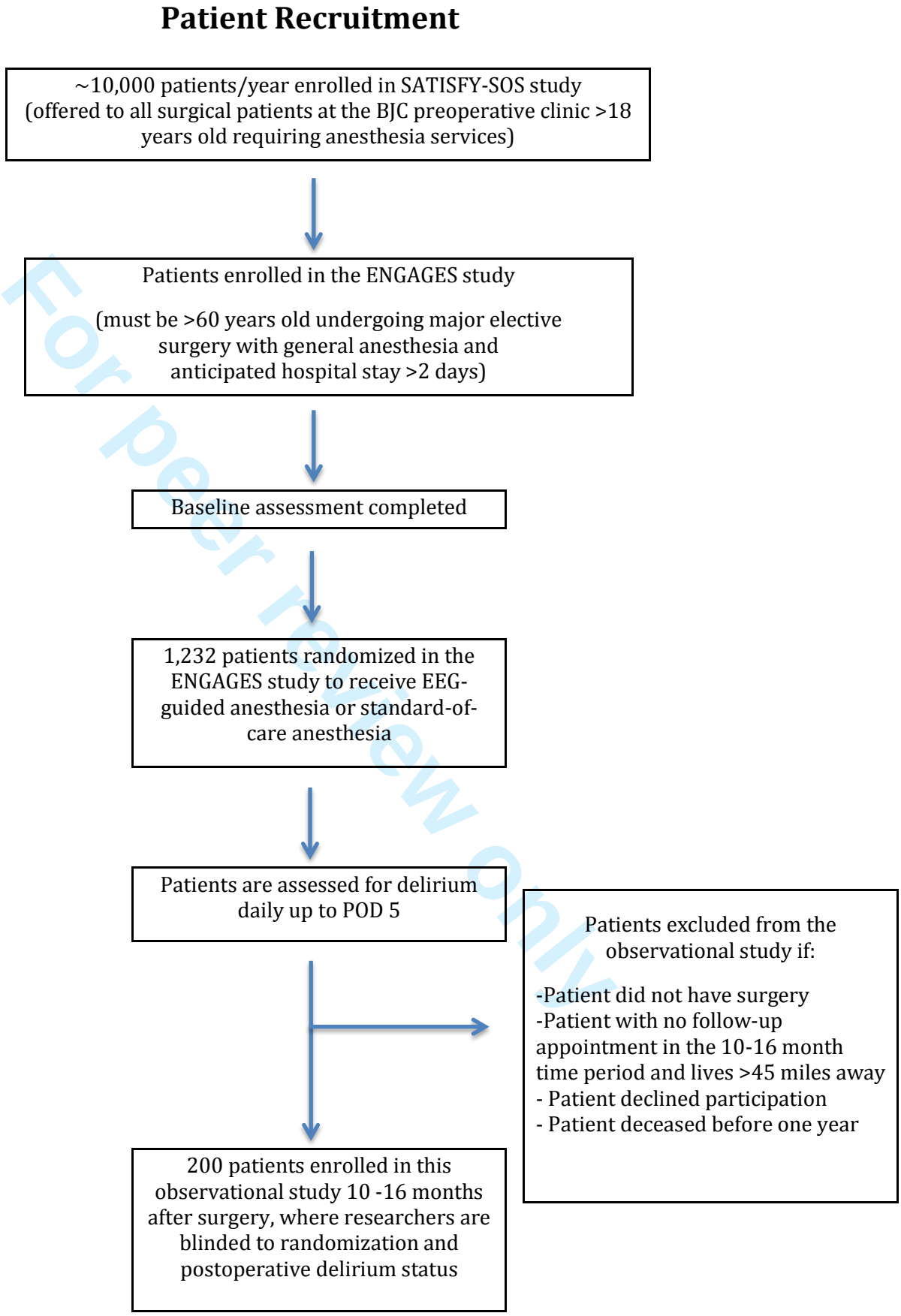
Appendix B.



STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page Number
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	N/A
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	2-4
Objectives	3	State specific objectives, including any prespecified hypotheses	4-5
Methods			
Study design	4	Present key elements of study design early in the paper	5-6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	6-7
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-7
Bias	9	Describe any efforts to address potential sources of bias	9-10
Study size	10	Explain how the study size was arrived at	9
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8-9 and table
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8-9
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	8
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	8-9

(*e*) Describe any sensitivity analyses

Continued on next page

Results			**Page Number**
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	N/A
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	N/A
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	N/A
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	N/A
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key results	18	Summarise key results with reference to study objectives	N/A
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	N/A
Generalisability	21	Discuss the generalisability (external validity) of the study results	
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Ability of postoperative delirium to predict intermediate-term postoperative cognitive function in patients undergoing elective surgery at an academic medical center: protocol for a prospective cohort study

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Primary Subject Heading:	Anaesthesia
Secondary Subject Heading:	Geriatric medicine, Neurology
Keywords:	postoperative delirium, postoperative cognitive decline, EEG guidance, quality of life, Dementia < NEUROLOGY, frailty

Title: Ability of postoperative delirium to predict intermediate-term postoperative cognitive function in patients undergoing elective surgery at an academic medical center: protocol for a prospective cohort study

Short title: Postoperative delirium predicting intermediate-term post-operative cognitive function

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Keywords: postoperative delirium, postoperative cognitive decline, EEG guidance, quality of life, dementia, frailty

Abstract

Introduction: Postoperative delirium (POD) is a common complication in elderly patients, characterized by a fluctuating course of altered consciousness, disordered thinking and inattention. Preliminary research has linked POD with persistent cognitive impairment and decreased quality of life. However, these findings maybe confounded by patient co-morbidities, postoperative complications, and frailty. Our objective is to determine whether POD is an independent risk factor for persistent impairments in attention and executive function after elective surgery. Our central hypothesis is that patients with POD are more likely to have declines in cognition and quality of life one year after surgery compared with patients without POD. We aim to clarify whether these associations are independent of potentially confounding factors. We will also explore the association between POD and incident dementia.

Methods and Analysis: This study will recruit 200 patients from the ongoing Electroencephalography Guidance of Anesthesia to Alleviate Geriatric syndromes (ENGAGES) study. Patients who live ≤45 miles from the study center or have a planned visit to the center 10-16 months postoperatively will be eligible. Patients with POD, measured by the Confusion Assessment Method, will be compared to patients without delirium. The primary outcome of cognitive function and secondary outcomes of quality of life and incident dementia will be compared between cohorts. Cognition will be measured by Trails A&B and Stroop Color Word Test, quality of life with Veteran's RAND 12-item Health Survey, and incident dementia with the Short Blessed Test. Multivariable regression analyses and a Cox proportional hazards analysis will be performed. All results will be reported with 95% confidence intervals and α=0.05.

Ethics and Dissemination: The study has been approved by the Washington University in St. Louis Institutional Review Board (IRB #201601099). Plans for dissemination include scientific publications and presentations at scientific conferences.

Trial registration: This is a pre-specified sub-study of ENGAGES (NCT02241655).

Strengths and Limitations of this study:

Strengths:

- Postoperative intermediate term cognitive function and quality of life are important patient-centered outcomes.
- Analysis will include salient patient characteristics, including preoperative cognition, comorbid conditions and frailty.
- Study sample will consist of an understudied population in clinical research.

Limitations:

- Potential for loss to follow-up and non-response bias
- Since this is an observational study, we cannot establish a causal relationship between postoperative delirium and persistent declines in cognition and quality of life.
- We cannot determine whether cognitive function deviates from the pre-operative trend, without multiple preoperative cognitive assessments to establish a trajectory.

Background

Since Bedford's 1955 case series suggesting an association between surgical intervention and cognitive impairment, there has been growing concern among the public that cognitive decline is a common consequence of surgery.[1] This pervasive view continues to concern patients and their families, fueled by anecdotal evidence and media coverage. Postoperative cognitive decline (POCD) has been a growing topic for scientific investigation after several studies were published by the International Study of Post-Operative Cognitive Dysfunction (ISPOCD) group. While several influential studies demonstrated early postoperative cognitive decline (POCD) lasting up to 3 months, the persistence of this cognitive decline has been controversial.[2-6] Importantly, the population of Americans older than 60 years is projected to double over the next 30 years,[7] and many will require surgery. Acute and long-term cognitive changes related to surgical intervention are particularly distressing to patients and their families. Therefore, clarification of cognitive outcomes would assist patients and practitioners in making an informed decision about the relative risks and benefits of proceeding with elective surgery.

Literature search and review

A systemized literature review was conducted with the help of a librarian experienced in systemic review (see Acknowledgement). Ovid Medline was searched for studies published between 1981 and September 2016 using the query: Postoperative or after surgery AND Delirium AND Cognitive function or dementia AND Elderly AND Long-term or intermediate term or follow up or cohort studies or retrospective studies. Articles in English or with English translation were considered. JC and RT reviewed the 301 search results and found 28 articles that were relevant to our clinical question. 21 out of the 28 relevant articles (75%) showed significant result in the relationship between postoperative delirium

(POD) and intermediate- to long-term cognitive decline (Appendix A). These seem to suggest a high pre-test probability in studying the ability of POD to predict intermediate-term cognitive decline. However, these studies are heterogeneous in the study design, selected surgical patient population, and outcome measurement tools complicating synthesis of the systemic search to draw conclusions.

POD is a common complication for surgical patients over the age of 60 years.[8] It is a neurological syndrome characterized by acute and fluctuating disturbances in awareness and attention that represent a change from baseline; in addition to these cardinal features, the diagnosis of delirium requires at least one additional cognitive symptom and the absence of medical conditions that might explain these disturbances.Although usually transient, POD has been associated with several salient adverse outcomes, including mortality, prolonged ICU stay and persistent cognitive decline.[9-12] One prospective cohort study of cardiac surgery patients suggested patients experiencing POD had prolonged cognitive impairment at one year, and those with longer duration of delirium had slower recovery.[12] However, after adjusting for baseline differences in cognitive function, there was no significant difference compared with controls. The same study also demonstrated that mild cognitive impairment preoperatively may predispose patients to delirium; thus POD may be exposing patients who are already experiencing sub-clinical cognitive decline or those who have an underlying vulnerability to cognitive decline. Another study, in orthopedic surgery patients found no association between POD and cognitive decline at three months.[13] While several studies have suggested that postoperative cognitive decline can persist past six months after surgery,[2, 14] others have demonstrated a transient early decline with later recovery.[4, 5] Furthermore, there is conflicting evidence regarding the long-term cognitive trajectories of postoperative patients, with some suggesting overall improvement and others suggesting overall decline.[15, 16] POD has been posited as a risk factor for lasting decline; however, few articles have addressed the association between POD and persistent postoperative cognitive decline (arbitrarily defined as lasting >6 months). A prospective matched controlled survey with an average of 30-month follow-up demonstrated that dementia or mild cognitive impairment was diagnosed in 77.8% of the surviving hip surgery patients with POD, almost doubling the 40.9% rate of control patients (relative risk = 1.9, 95% CI = 1.1-3.3). However the study was underpowered to evaluate the long-term cognitive function, as the power calculation was based on the original study and no intermediate assessments were made to track patients' cognitive function.[17] Another prospective cohort study followed patients over 36 months and found that patients with POD initially had cognitive decline with a transient recovery, but then exhibited an accelerated pace of long-term cognitive decline when compared to controls.[18] Overall, the results of these studies suggest an association between POD and persistent cognitive impairment, however compelling data supporting an independent association are lacking. Many of these studies also do not consider the duration of delirium, which may portend long-term cognitive decline.[19, 20]

Pre-existing dementia or cognitive impairment is a known risk factor for POD,[8] and several studies suggest an association between POD and dementia. One study in elderly orthopedic surgery patients reported a relative risk of dementia in patient with POD of 10.5 compared to those without POD.[21] A recent study demonstrated a similar association in elderly cardiac surgery patients.[22] However it remains unclear whether POD causes, accelerates, or signifies an underlying vulnerability to cognitive impairment, thus further investigation is warranted.

In addition to cognitive outcomes, quality of life and functional capacity are also important patient-centered outcomes that require further investigation. While one study found that elderly surgical patients tended to have long-term cognitive and functional decline compared to non-surgical patients,[23] few studies have examined the association between cognitive function and quality of life or activities of daily living. One prospective study over a 10-month period demonstrated that delirium

was an independent risk factor for becoming dependent for personal activities of daily living after ICU discharge (OR = 2.188, P <0.046) and that patients with POD also demonstrated a greater decline in Short-Form-36 domains after discharge, especially in physical function, vitality, and social function.[24] However, this study could not draw conclusions regarding cognitive function due to lack of data. Kastaun et al. reported perceived impairment in ability to perform activities of daily living one year after surgery, however did not detect significant cognitive decline at that time.[25] It remains unclear whether cognitive decline results in impaired functional capacity or decreased quality of life. In fact, given the variable definitions of POCD, data from previous studies are difficult to interpret. As many of the deficits found in neuropsychiatric testing are subtle, it is possible that detected cognitive impairment has no clinically significant impact on these patient-centered outcomes. Instead of using an arbitrary threshold to dichotomize cognitive function as normal or impaired, it would be more informative to correlate these outcomes with cognitive function as a continuous variable or stratified into multiple groups.

At our institution, patient reported postoperative outcomes are gathered as part of the Systematic Assessment and Targeted Improvement of Services Following Yearlong Surgical Outcomes Surveys (SATISFY-SOS) initiative (NCT02032030). Additionally, the ongoing randomized controlled trial: Electroencephalography (EEG) Guidance of Anesthesia to Alleviate Geriatric syndromes (ENGAGES) study, is evaluating patients for postoperative delirium.[26] Using the scaffold provided by these studies, we aim to identify whether delirium is an independent predictor for intermediate-term cognitive function and quality of life.

Justification

The population of older adults is projected to double over the next thirty years, and many will undergo elective surgery with the hope of overall improvement in health and quality of life. Postoperative delirium is a common and potentially preventable complication, thus clarification of its association with persistent declines in cognition and quality of life will inform perioperative care. Prior studies have not demonstrated an association independent of pre-existing patient characteristics and perioperative course. The proposed study addresses the methodologic concerns in current literature by: 1. objectively evaluating attention and executive function with validated cognitive tests, 2. obtaining measurements of baseline cognitive function, 3. conducting statistical analysis which includes important potential confounding factors including frailty measures, and 4. sampling from an unselected surgical population. Given that delirium is predominantly a disorder of attention and executive function, we will focus our investigation on these cognitive domains. The results of this study will contribute to the broader understanding of postoperative cognitive changes, and may help identify and provide therapies for susceptible patients earlier to ultimately improve outcomes.

As part of the ENGAGES study, patients have been enrolling since January 2015, with 804 patients enrolled thus far. Over the last year, the ENGAGES research team has enrolled approximately 35 patients per month, and has gathered baseline cognitive data on a majority of participants. Preliminary screening suggests about 65% of those enrolled in ENGAGES are eligible for the current study. Anticipating that half of those contacted will enroll, we expect to assess 10 to 15 patients per month. The scaffold of ENGAGES and trained study members make this sub-study highly feasible.

Specific Aims

Specific Aim #1: Determine whether the incidence and duration of postoperative delirium predict worse performance on specific cognitive tests at approximately one year after surgery.

We hypothesize that postoperative delirium is independently associated with poorer performance on tests of attention and executive function at one year after surgery, and that patients with a longer duration of delirium will have more marked cognitive decrement. We will conduct a regression analysis, including likely contributory variables, to assess the association between delirium and cognitive decline at approximately one year.

Specific Aim #2: Evaluate whether the incidence and duration of postoperative delirium predict worse quality of life at approximately one year postoperatively.

We hypothesize that postoperative delirium is independently associated with decreased quality of life one year after surgery, and that patients with a longer duration of delirium will have more marked decrease in health-related quality of life. We will conduct a regression analysis, including likely contributory variables, to assess the association between delirium and health-related quality of life at approximately one year.

Specific Aim #3: Explore whether patients who experience postoperative delirium are more likely to develop dementia within approximately one to two years of their surgery.

We hypothesize that postoperative delirium is independently associated with incident dementia one to two years after surgery. We will conduct a Cox proportional hazards regression, including likely contributory variables, to assess the rate of incident dementia approximately one to two years after surgery.

Study Design:

This prospective cohort study is pre-specified sub-study of the ENGAGES study. The ENGAGES study is a randomized clinical trial enrolling approximately 1,200 patients sixty years and older who will undergo elective major surgery at Barnes Jewish Hospital (BJH), St. Louis, MO.

The parent trial will recruit patients primarily from the Center for Preoperative Assessment and Planning (CPAP) clinic. Among inclusion criteria for ENGAGES, details of which have been previously published,[26] is enrollment in the SATISFY-SOS study.[27] As part of ENGAGES, participants will complete a comprehensive baseline assessment including cognitive tests, frailty measures, and screening for delirium and dementia. Postoperatively, patients will have daily evaluations for delirium during the hospital stay. The current study will retrospectively identify 200 participants who reside within approximately 45 miles from the hospital or those who have a planned visit to the hospital between ten to sixteen months post-operatively. Patients diagnosed with delirium postoperatively will be compared to those without delirium. A prospective intermediate-term postoperative assessment will be conducted by a research team member blinded to whether the patient developed postoperative delirium.

Study Groups

The target population for this study is patients who underwent preoperative assessment for elective surgery at the Center for Preoperative Assessment and Planning (CPAP) clinic at Barnes Jewish Hospital (BJC) in St. Louis, Missouri. The ENGAGES study is enrolling 1,232 patients who are already enrolled in the STATISFY-SOS study. Inclusion criteria include patients sixty 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 two days postoperatively (i.e., 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). The ENGAGES study has minimal exclusion, as there are no absolute contraindications to EEG monitoring. Exclusion criteria include neurosurgical procedures, preoperative delirium, patients who are unable to participate adequately in delirium screening, including those who are blind, deaf, illiterate, or not fluent in English, patients with a history of intraoperative awareness during intended general anesthesia, and patients who had a second surgery planned within five days after the index surgery. This prospective study will enroll 200 patients who are already enrolled in the ENGAGES and SATISFY-SOS studies (Appendix B). In addition to previously described inclusion and exclusion criteria, participants will be included in this study if their home residence is ≤45 miles from BJH or they have a planned visit to the hospital within the specified timeframe. Patients who have not completed the baseline cognitive assessment with Trails A, Trails B and the Stroop Color Word Test will also be excluded from this study.

Recruitment

As part of the SATISFY-SOS study, patients have given informed consent to be contacted by Washington University for follow-up of health-related outcomes up to a year after surgery. Eligible participants will be identified by chart review and query of the ENGAGES REDCap database. A member of the research team will contact potential participants by telephone approximately ten to sixteen months after surgery for enrollment in this study. Patients may refuse participation in the study. If patients agree to participation, written consent will be obtained when the patient comes in for assessment, prior to any data collection. Patients will then be prospectively evaluated with assessments of cognition, quality of life, and frailty measures, which are described in detail below. Meal vouchers will be provided for participation. Patients residing within approximately 45 miles of the hospital, who are willing to participate in the study, but unable or unwilling to come to the study center will be offered assessment at home by a member of the research team. Additionally, ENGAGES patients who have not completed a one-year dementia screening will be contacted by telephone approximately 18 to 24 months after surgery. Phone consent will be obtained to complete dementia screening over the telephone. Participants may refuse to participate.

Data

Data Collection

Routinely obtained baseline assessment in the CPAP clinic includes demographic information, a detailed medical history, surgical history, medications and physical examination. As part of SATISFY-SOS and ENGAGES, baseline assessment using the Barthel Index, Veteran's RAND 12-item Health Survey (VR-12), Eight-item Interview to Differentiate Aging and Dementia (AD-8), Short Blessed Test (SBT), alcohol sniff test, and Personal Health Questionnaire Depression Scale (PHQ8) will be performed. Baseline cognitive

function will be evaluated by the ENGAGES team with the Trails A and B, and the Stroop Color and Word Test. Some patients may complete computer-based cognitive testing with the NIH toolbox at baseline (described below). Additionally, frailty will be assessed using grip strength, Timed-up and Go (TUG) test, and obtaining fall history at baseline. Participants will have daily delirium assessments by trained researchers with the Confusion Assessment Method in the postoperative period for the duration of their hospital stay. Data collected by the ENGAGES team will be entered into the Washington University School of Medicine Research Electronic Data Capture (REDCap) application. [18] Perioperative data will be retrieved from the hospital's perioperative electronic medical record (Metavision by iMDsoft®, Needham, MA). High fidelity perioperative data is routinely captured from our EMR to an SQL server (Microsoft, Redmond, WA) database. These data include bispectral index (BIS) values, EEG burst suppression durations, laboratory data, intraoperative medications, physiological readings, and postoperative recovery parameters. 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.

Cognition: The primary outcome in this study will be a composite score comprised of scores from three cognitive tests evaluating attention and executive function: Trails A, Trails B and Stroop Color Word Test. These cognitive tests will be repeated approximately one year after surgery to evaluate intermediate term cognitive function. The research team member performing the assessments will be blinded to whether the patient developed postoperative delirium. In addition to the above tests, this study proposes to use the Cognition Battery of the National Institutes of Health (NIH) Toolbox Assessment of Neurological and Behavioral Function (http://www.nihtoolbox.org). The NIH Toolbox Cognition Battery (Feinberg School of Medicine, Northwestern University, Chicago, IL), is a comprehensive yet concise standardized computer-based assessment battery; we plan to include tasks to evaluate attention (Flanker Inhibitory Control and Attention Test), episodic memory (Picture Sequence Memory Test),and executive function (Dimensional Change Card Sort Test and Flanker Inhibitory Control and Attention Test). Patients will complete the NIH Toolbox Cognition tests above, which takes approximately 10 minutes to complete. The NIH Toolbox Cognition Battery has been validated for use across a wide range of ages.[28, 29] Self-reported cognitive function will be evaluated by The Patient Reported Outcomes Measurement Information System (PROMIS). PROMIS, funded by the National Institutes of Health (NIH), is a set of highly reliable, valid, flexible, precise, and responsive assessment tools that measure patient–reported health status. PROMIS v1.0-Applied Cognition-General Concerns-Short Form 4a is comprised of four questions about thinking and cognition. PROMIS v1.0-Applied Cognition-Abilities-Short Form 4a is comprised of four questions about memory. Evaluation for dementia with the SBT will be completed for all patients at baseline, and again between one to two years after surgery. The SBT has been shown to have 95% sensitivity for detecting cognitive dysfunction when compared with the MMSE, and can be administered in approximately 3 minutes, making it an excellent screening tool.[30]

Quality of Life: As part of the ongoing SATISFY-SOS study, patient self-reported Health-related Quality of Life information will be assessed through the VR-12 at baseline (preoperatively) and also one year after surgery. The VR-12 was derived from the Veterans RAND 36 Item Health Survey (VR-36) and contains twelve 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.[31]

Functional status: We will assess functional status with the Barthel Index for Activities of Daily Living and Lawton Instrumental Activities of Daily Living Scale. The Barthel Index is a measure of patient

performance in ten activities comprised of eight questions about personal care and two questions about mobility. The Lawton Scale assesses independent living skills in 8 areas of function.

Frailty: Information regarding weight loss, endurance, and physical activity level are routinely collected in the preoperative clinic and as part of SATISFY-SOS. We will also measure grip strength and the Timed Up and Go (TUG) test. Grip strength will also be assessed with three measurements in the dominant hand using a Jamar® handheld dynamometer (Lafayette Instruments, Lafayette, IN). Maximal grip strength will be selected for analysis.

Table 1. contains details regarding variables to be collected for the study.

Data management

A customized database has been developed to facilitate data management for this study using the Research Electronic Data Capture (REDCap) system. REDCap is a secure web-based data capture system available to research groups receiving support from the Institute of Clinical and Translational Sciences at Washington University. It is maintained by the Washington University Division of Biostatistics with multiple capabilities to simplify data management and analysis. These include intuitive data entry, data audit and tracking, import of externally sourced data, and automated data export for analysis. REDCap requires unique user identification and password combinations for secure access.

Statistical Consideration

Sample calculations

For specific aims 1&2, sample size calculations have been performed using G*POWER 3.0.10. Power analysis for a multiple regression with 15 predictors was conducted to determine a sufficient sample size using an alpha of 0.05, a power of 0.9, and a medium effect size ($f^2 = 0.1$). Based on the aforementioned assumptions, the desired sample size is 130 patients. We will plan to recruit 200 patients, which will increase the power for the primary outcome and prevent overfitting of the regression model.

For specific aim 3, sample size calculation has been performed using PS 3.1.2. 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 POD of 25%. A previous study has reported the median age at the onset of dementia to be approximately 84 years old.[32] To detect a hazard ratio of 2.0 in patients with delirium compared to those without delirium, with 80% power and α=0.05, we will need 516 patients (129 in the delirium group, and 387 in the control group). To account for a 10% attrition rate, we will recruit 570 patients.

Statistical analysis

We will perform and report descriptive statistics (mean and standard deviation) for all variables between patients with and without the diagnosis of POD. Descriptive statistics will include chi-squared tests for categorical variables, t-tests for normally distributed continuous variables and Mann-Whitney tests for nonparametric continuous variables.

Specific Aim 1: Determine whether patients who experience POD perform worse on specific cognitive tests at approximately one year after surgery.

The primary endpoint of our analysis is cognitive function one year after surgery, as measured by the Trails A &B and the Stroop Color Word Test. Z-scores will be calculated for performance for each test, and combined to form a composite measure. Multivariable regression analysis will be used to determine whether the development of postoperative delirium is a predictor variable for cognitive function, independent from other possible contributory factors. POD will be entered as two categorical variables: for incidence (present or absent) and for duration (<3 days POD or ≥3 days POD). The following variables will be included in the model: age, sex, American Society of Anesthesiologists physical score, and Charlson co-morbidity index. The following known or suggested risk factors cognitive decline will also be included in the model: baseline cognitive function, education level, type of surgery, randomization group, preoperative depression, preoperative vascular disease, postoperative complications, composite score on frailty tests and a history of falls. We will use a model with backward elimination, to avoid exclusion of predictors with suppressor effects. While cognition will be entered as a continuous variable, we will consider a change of one standard deviation in cognitive score as a minimal clinically important difference.

Specific Aim 2: Evaluate whether patients who experience POD have worse quality of life at approximately one year postoperatively.

The primary endpoint of our analysis is quality of life one year after surgery, as measured by the change in VR-12 score between preoperative and postoperative assessments. Again, a multivariable regression analysis will be performed to evaluate whether the development of postoperative delirium is an independent predictor variable for the change in quality of life. POD will be entered as two categorical variables: for incidence (present or absent) and for duration (<3 days POD or ≥3 days POD). The following variables will be included in the model: age, sex, American Society of Anesthesiologists physical score, Charlson co-morbidity index, type of surgery, randomization group, preoperative depression, preoperative vascular disease, postoperative complications, cognitive function, composite score on frailty tests and a history of falls. As above, we will use a model with backward elimination, to avoid exclusion of predictors with suppressor effects. Previous work by our group has calculated the minimal clinically important difference for overall VR-12 quality of life to be 1.4 for improvement and 3.6 for deterioration.[33]

For the above aims, we expect this study to be limited by loss to follow-up, estimated to be 50%. Those lost to follow-up are likely to have more severe disease or deterioration in health. In order to determine the influence of missing data in our analysis, we will also conduct a sensitivity analysis. We will calculate the average cognition scores of those who declined. We will repeat the above models including missing subjects, assuming all patients who did not participate had cognitive decline, quantified by the average calculated from participants above. Additionally, to examine whether our sample selection method may bias the results, we will compare baseline characteristics of those ENGAGES patients who were eligible for our study to those who were not eligible.

Specific Aim 3: Explore whether patients who experience POD are more likely to become demented within approximately one to two years of their surgery.

The primary endpoint of our analysis is incident dementia. A Cox proportional hazards regression will be used to explore the likelihood of incident dementia associated with POD. POD will be entered as a dichotomous variable (absent or present). The following variables will be included in the model: age, sex, American Society of Anesthesiologists physical score, Charlson co-morbidity index, preoperative cognitive function, type of surgery, randomization group, preoperative depression, preoperative vascular disease, postoperative complications, and composite score on frailty tests and a history of falls.

All statistical analyses will be performed using SAS, version 9.4 (SAS Institute, Inc., Cary, North Carolina). All other tests will be two-sided. By arbitrary convention all tests will be two-sided and considered statistically significant at a $p<0.05$, and all results will be presented with estimates and 95% confidence intervals.

Pre-specified additional analyses and sub-studies

The primary aim of this study is to determine whether postoperative delirium predicts intermediate-term cognitive impairment. However, as a sub-study of ENGAGES and SATISFY-SOS, several other clinically relevant outcomes can be explored as well. SATISFY-SOS systematically collects detailed information regarding patient centered outcomes, including patient perceived cognition. Correlation between performance on neurocognitive testing and patient perceived cognition would be interesting and useful clinically. Furthermore, the information regarding patients' characteristics will allow exploration of risk factors for intermediate-term cognitive impairment. To investigate effects on memory, we will perform a secondary analysis comparing the results of the SBT. Lastly, as part of ENGAGES, some patients will have baseline NIH Toolbox cognitive testing, allowing description of long-term cognitive trajectories as evaluated by these tests.

Limitations

This study contains several limitations. First, of most concern is the potential for non-response bias if patients who do not participate are not a random subset of those contacted. We will attempt to minimize the non-response rate by offering to visit patients at their homes if patients are unwilling to come to the study center. We expect that those lost to follow-up would be more likely to have more severe disease or health deterioration, potentially affecting cognitive function. We will thus conduct appropriate sensitivity analyses to determine how missing outcomes data could alter the findings of our study. Second, with an observational study, we cannot establish a causal relationship between postoperative delirium and persistent declines in cognitive and quality of life. If an independent relationship is found, we shall not be able to disambiguate whether postoperative delirium in some way causes persistent decline in these outcomes, or whether it is a sign of underlying vulnerability. However, since it is not possible to randomize patients to experience delirium, this limitation might be inevitable. Third, since patients in this study are recruited from a single tertiary care center, the study sample may not be representative of surgical patients in general. While these patients tend to have higher comorbid disease burden then the general surgical population, including comorbidities in the statistical model will account for these differences. Finally, while we have baseline cognitive assessments, we do not have preoperative cognitive trajectories, and thus cannot determine whether the results of cognitive function tests are a deviation from the pre-operative trend.

Compliance

Subject Compliance

The exposure of this study is post-operative delirium, so no monitoring of exposure compliance is necessary. Methods to improve completion of one-year cognitive testing are described in Section 10.3, "Limitations."

Withdrawal of subjects

Subjects may be withdrawn from the study only if requested by the patient. The reason for withdrawal is recorded by the team's clinical project specialist.

Ethical Considerations

This study has been approved by the home institution's Institutional Review Board (IRB ID # 201407128). Written, informed consent is obtained from all participants. As described in Section 7, "Study Groups," no special allowances are made for patients who are blind, deaf, illiterate or not fluent in English. Participants may withdraw from the study at any time.

Finance and Insurance

Since this study involves only cognitive testing and surveys, it involves no more than minimal risk to the patients. Finance details, insurance details, and cover for negligent and non-negligent harm are therefore not relevant in this study.

Reporting and Dissemination

Results of this study will be published in a scientific journal. Participants will only be notified individually if discoveries are made that directly impact their health. We intend to make deidentified individual participant data used to obtain the results reported from this study available to researchers providing a study proposal between three months and five years after article publication. This study protocol, the statistical analysis plan and analytic code will also be available.

Author Contributions

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. MSA, AA, JZC, MM, RT, TW, EL are responsible for conceptualizing study design. AA, JZC, RT, MM, HM, and AM were responsible for recruitment, enrollment, data collection and editing the protocol. AA, JZC, and RT are responsible for drafting the protocol. All authors including AA, JZC, MM, RT, AM, HM, NL, TW, EL, and MSA have critically revised the protocol and approved the final version.

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Competing Interests

The authors and contributors have no competing interests to disclose.

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Table 1

Type	Variable	Form	Source	Time	Standardized Tool?
Explanatory	Postoperative delirium incidence	Dichotomous (present or absent)	ENGAGES postoperative assessment	Inpatient postoperative hospital days	Yes
	Postoperative delirium duration	Categorical (<3 days or ≥3 days)	ENGAGES postoperative assessment	Inpatient postoperative hospital days	N/A
	Charlson Comorbidity Index	Ordinal, 0 to 12	Medical record	Baseline	Yes
	Weight loss ≥ 10 lbs	Dichotomous	Medical record	Baseline	N/A
	Functional capacity	<4, 4-6, 6-10, >10 metabolic equivalents	Medical record	Baseline	Yes
	Physical activity level	<4, 4-6, 6-10, >10 metabolic equivalents	Medical record	Baseline	Yes
	Grip Strength	Continuous	Research team member	Baseline and one year	Yes
	Timed Up and Go	Continuous	Research team member	Baseline and one year	Yes
	History of falls	Dichotomous	Survey	Baseline	N/A
	Postoperative Complications	0, 1, 2, 3+	Survey and medical record	One year	No
	ASA Physical Status	Ordinal, 1 to 6	Anesthesia record	Baseline	Yes
Outcome	Trails A	Continuous	Research team member	Baseline and one year	Yes
	Trails B	Continuous	Research team member	Baseline and one year	Yes
	Stroop Color Word Test	Continuous	Research team member	Baseline and one year	Yes
	Physical quality of life	Continuous	Survey	Baseline and one year	Yes
	Mental Quality of life	Continuous	Survey	Baseline and one year	Yes
	Dementia	Dichotomous	Survey	Baseline and one year	Yes
Confounder	Age	Continuous	Medical record	Baseline	N/A
	Sex	Dichotomous	Medical record	Baseline	N/A
	Education level	< High school, High school,	Research team member	Baseline	N/A

		>High school			
	Functional dependence	Ordinal, 0 to 100	Research team member	Baseline and one year	Yes
	Depression	Dichotomous	Medical record and survey	Baseline and one year	Yes
	Preoperative vascular disease	Dichotomous	Medical record	Baseline	No
	Type of surgery	Ten categories	CPAP assessment	Baseline	N/A
	ENGAGES randomization	Dichotomous	Research team member	Day of surgery	N/A

Appendix A.

Protocol Literature Review

Author	Study Design	Sample size	Patient Pop.	Outcomes	Assessment	Follow-up	Results
Tow et al[1]	Prospective cohort	142	Older adults undergoing elective orthopedic surgery	Incidence and severity of POD	CAM, Memorial Delirium Assessment Scale, cognitive reserve (literacy and cognitive activities)	First assessment median 22 hrs postoperatively, second assessment median 32 hrs postoperatively	Greater participation in cognitive activity was associated with lower incidence and severity of delirium
Neufeld et al[2]	Prospective cohort	91	Consecutive patients undergoing surgical procedure, ≥ 70 y/o	Cognitive functioning	ADLs, IADLs, MMSE, Word Fluency, Digit Span, DSM-IV delirium criteria	19 months postoperatively	No differences in any outcomes between patients with versus without PACU delirium
Sprung et al[3]	Population based prospective cohort	1,731	70-89 y/o (data abstracted retrospectively for anesthesia exposure from 40 years old until time of evaluation)	Mild cognitive impairment	1) impairment in one of the four cognitive domains; 2) cognitive concerns by the subject, informant, examining nurse, or physician; 3) essentially normal functional activities, and; 4) absence of dementia (based on published criteria)	Median 4.8 years	31% developed MCI; Cumulative exposure to procedures requiring GA after the age 40 was not associated with the development of incident MCI in cognitively normal elderly participants. Does not exclude possibility that anesthetic exposures occurring later in life may be associated an increase in the rate of incident MCI, especially in patients undergoing vascular surgery
Hempenius et al[4]	RCT	260	Consecutive patients ≥65 years undergoing surgery for a solid tumor	mortality, rehospitalization, ADL functioning, return to the independent pre-operative living situation, use of supportive care, cognitive functioning and health related QOL	DOS for delirium, MMSE for cognition	3 months	Geriatric liaison intervention did not improve outcomes. POD was associated with: an increased risk of decline in ADL functioning, an increased use of supportive assistance, and a decreased chance to return to the independent preoperative living situation.
Youngblom et al[5]	Prospective cohort	421	>65 y/o, noncardiac surgery	Delirium and POCD	For delirium: CAM; for POCD: verbal fluency, digit	2 days postop	80% of patients experienced delirium or POCD on POD1. 48%

					symbol test, and word list		experienced postoperative delirium on POD1, POD2, or both days. The delirium group had a lower preoperative cognitive status score. incidence of pre-existent dementia was not different between the group that developed delirium and the group that did not.
Hussain et al[6]	Review	N/A	N/A	Relationship between general anesthesia, major surgery, and dementia, specifically AD	N/A	N/A	Future studies need: sufficient sample size, good control group (no anesthesia, no surgery, well-matched otherwise), preop cognitive assessment, maybe use biomarkers for AD.
Abelha et al[7]	Prospective	562	SICU patients	Primary: Mortality Secondary: hospital mortality and "becoming dependent"	ICDSC for postoperative delirium, SF-36 for health-related QOL	6 months	POD is an independent risk factor for mortality, hospital mortality, and becoming dependent for personal ADLs. Delirium incidence: 16%
Witlox et al[8]	Prospective cohort nested w/in RCT	53	≥75 years old, hip fracture repair	Delirium and postoperative cognitive decline	Delirium: CAM Cognition: MMSE, the expanded digit span test, and the GDS	3 months	All pts who developed delirium were asked to f/u and an equal number of control pts invited to f/u as well; 5 patients still delirious at 3 months; delirium was associated with impairments in global cognition and episodic memory at follow-up
Radtke et al[9]	RCT	1155	≥60 y/o with at least 60 minute surgery with general anesthesia	Delirium and postoperative cognitive dysfunction	Delirium: DSM IV delirium criteria Cognition: Motor Screening Test, two tests of visual memory and a test of attention, visual verbal learning test and the Stroop Color Word interference test	Assessed for delirium while admitted, f/u at 1 week and 3 months	Delirium incidence was lower in the BIS-monitored group (16.7 vs 21.4%), but POCD was not different in the BIS vs non-BIS group.
Saczynski et al[10]	Prospective cohort	225	>60 y/o, undergoing CABG or	Delirium and cognition	Delirium: CAM; Cognition: MMSE	Delirium assessed starting POD2	Delirium incidence: 43%; Those who developed delirium has a lower

			valve replacement			until pt discharge; Cognitive tests preop and at 1, 6, and 12 months postop	preoperative cognitive score.
Koster et al[11]	Prospective follow-up study	300	>45 y/o undergoing elective cardiac surgery	Delirium, postoperative cognition and functionality, Mortality, readmission	Delirium: DOS scale; Cognition: SF-36, the Cognitive Failure Questionnaire, and a purpose-designed questionnaire	6 months	Delirium incidence: 17%; Delirium was associated w/increased mortality, a higher hospital readmission rate, lower quality of life, cognitive failure, and reduced mobility.
Quinlan et al[12]	Secondary analysis of prospective study	1218 (948 completed 3 month functional assessment)	Non-cardiac surgery, ≥ 60 y/o	Delirium, cognition, POCD	MMSE, chart review, ISPOCD neuropsychological tests	3 months postoperatively	After adjustment for age, sex, education, cognition, and surgery duration, delirium remained associated with functional decline
Wallbridge et al[13]	Prospective cohort	89	Patients undergoing elective abdominal aortic aneurysm surgery y/o	Cognition and function	Battery of cognitive measures, Portland Adaptability Inventory (PAI) for function	3 months postoperatively	Cognitive impairment postoperatively was mild but was associated with number of days delirious and preoperative deficits in verbal memory and psychomotor speed
Jankowski et al[14]	Prospective cohort	418	≥ 65 y/o, undergoing total hip or knee arthroplasty	Delirium, cognition, function	CAM, MMSE, neurocognition and functional testing (American National Adult Reading Test, AVLT, COWAT, SCWT, CAGE, IADL)	3 months postoperatively	Independent predictors of POD included age, history of psychiatric illness, decreased functional status, and decreased verbal memory
Rudolph et al[15]	Prospective cohort	190	≥ 60 y/o, elective or urgent cardiac surgery	Delirium, activities of daily living (function)	CAM, IADL	1 and 12 months postoperatively	Delirium associated with functional decline at 1 month and tended toward association at 12 months
Koster et al[16]	Prospective cohort	112	Consecutive patients undergoing elective cardiac surgery, ≥ 45 y/o	Delirium, mortality, readmission, cognition, function	DSM-IV criteria, study designed questionnaire for cognition	1-1.5 years after surgery	POD associated with increased mortality, readmission, memory and concentration problems, and sleep disturbance

Gogol et al[17]	Review	N/A	N/A	Cognition, dementia, mortality, functional status	N/A	N/A	Delirium is associated with increased short- and long-term mortality, iatrogenic complications, functional decline, and future development of cognitive impairment or dementia.
Bickel et al[18]	Prospective cohort	200	Consecutive hip surgery patients ≥ 60 years old	Delirium, cognition, mortality, need for long term care	MMSE, CAM	8 to 38 months postoperatively	Delirium was a strong independent predictor of cognitive impairment and severe dependency in activities of daily living - more marked long- than for the short-term
Kat et al[19]	Prospective matched controlled cohort	112	Hip surgery patients ≥70 y/o	Delirium, dementia/mild cognitive impairment (MCI)	CAM, MMSE	30 months postoperatively	Delirium associated with increased risk of dementia/MCI, mortality, and institutionalization
Rudolph et al[20]	Prospective cohort	1218	Non-cardiac surgery, ≥ 60 y/o	Delirium, cognition, POCD	MMSE, chart review, ISPOCD neuropsychological tests	7 days and 3 months postoperatively	Delirium associated with early but not late POCD
Olofsson et al[21]	Prospective cohort	61	Consecutive patients undergoing femoral head fracture operation, ≥ 70 y/o	Delirium, LOS, activities of daily living	IADL, Cognition: MMSE, Delirium: OBS, Depression: GDS-15, PGCMS, S-COVS	4 months postoperatively	Delirium incidence: 68%. Delirium was associated with more dementia and depression before their fractures, longer LOS after surgery, and more dependence before surgery, on discharge, and at 4 month f/u.
Rothenhausler et al[22]	Prospective cohort	30	Patients undergoing cardiac surgery with CPB	Cognition, depression, posttraumatic stress symptoms, health status, delirium	Syndrom Kurztest, SF-36, Delirium Rating Scale (DRS)	1 year postoperatively	Lower cognition associated with lower HRQOL
Duppils et al[23]	Prospective cohort	115	≥ 65 y/o, prior participation in observational hip fracture - delirium study	Delirium, cognition, quality of life	DMS-IV criteria for delirium, MMSE, SF-36	6 months postoperatively	Delirium associated w/ greater cognitive deterioration in hospital, lower health-related quality of life at follow up
Edelstein et al[24]	Prospective cohort	921	≥ 65 y/o, operatively treated hip fracture	Postoperative complication rates, in-hospital		1 year follow up	POD incidence: 5.1%. Patients w/ POD had longer LOS, higher 1 year mortality, less likely to

				mortality, hospital LOS, hospital discharge status, 1-year mortality rate, place of residence, recovery of ambulatory ability, and activities of daily living			recover level of ambulation, more likely to show a decline independence. No difference in postoperative complications, in-hospital mortality, discharge residence, and recovery of instrumental activities of daily living at 1 year.
Adunsky et al[25]	Retrospective cohort	281	Elderly hip fracture patients	Cognition, delirium, function	MMSE, CAM, functional independence measure (FIM)	1 week postop and at discharge	Delirium patients tend to be more disabled and more cognitively impaired
Lundstrom et al[26]	Prospective cohort	78	≥ 65 y/o, non-demented, femoral neck fracture	Dementia and mortality	Organic Brain Syndrome (OBS) scale and MMSE	5 year follow up	Increased dementia and mortality in patients with POD vs. not
Edlund et al[27]	Prospective cohort	54	Consecutive patients admitted for femoral neck fractures, age range 40-98 y/o	Postoperative delirium incidence	OBS	6 months follow up	POD incidence: 27.8%. Dementia & increased surgery wait time = greater POD incidence; delirium = worse outcomes after surgery
Goldstein et al[28]	Prospective cohort	362	General surgical, orthopedic, non-surgical, ≥ 55 y/o	Postoperative decline	Psychosocial questionnaire, tests of cognition, affect, function	10 months postoperatively	No significant contribution to changes from baseline

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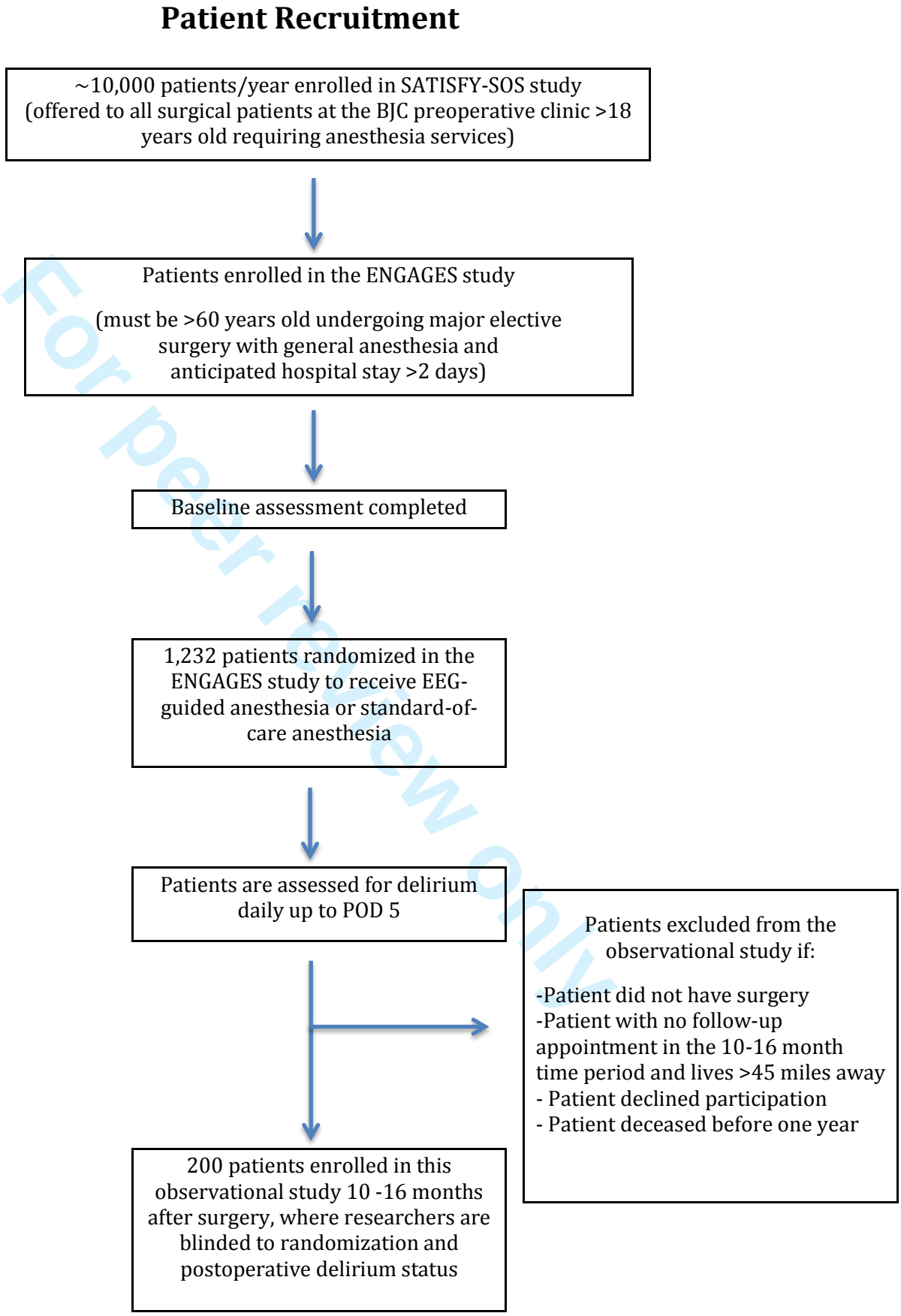
Appendix B.



STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page Number
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	N/A
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	2-4
Objectives	3	State specific objectives, including any prespecified hypotheses	4-5
Methods			
Study design	4	Present key elements of study design early in the paper	5-6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	6-7
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-7
Bias	9	Describe any efforts to address potential sources of bias	9-10
Study size	10	Explain how the study size was arrived at	9
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8-9 and table
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8-9
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	8
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	8-9

(*e*) Describe any sensitivity analyses

Continued on next page

Results			**Page Number**
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	N/A
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	N/A
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	N/A
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	N/A
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key results	18	Summarise key results with reference to study objectives	N/A
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	N/A
Generalisability	21	Discuss the generalisability (external validity) of the study results	
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.