

BMJ Open

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<http://bmjopen.bmj.com>).

If you have any questions on BMJ Open's open peer review process please email editorial.bmjopen@bmj.com

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2017-017079
Article Type:	Protocol
Date Submitted by the Author:	02-May-2017
Complete List of Authors:	Aranake-Chrisinger, Amrita; Washington University in Saint Louis School of Medicine, Anesthesiology Cheng, Jenny; Washington University in Saint Louis School of Medicine, Anesthesiology Muench, Maxwell; Washington University in Saint Louis School of Medicine, Anesthesiology; Kirksville College of Osteopathic Medicine, Tang, Rose; Washington University in Saint Louis School of Medicine, Anesthesiology Mickle, Angela; Washington University in Saint Louis School of Medicine, Anesthesiology Maybrier, Hannah; Washington University in Saint Louis School of Medicine, Anesthesiology Lin, Nan; Washington University in Saint Louis, Mathematics; Division of Biostatistics Wildes, Troy; Washington University in Saint Louis School of Medicine, Anesthesiology Lenze, Eric Avidan, Michael; Washington University School of Medicine, Anesthesiology
Primary Subject Heading:	Anaesthesia
Secondary Subject Heading:	Geriatric medicine, Neurology
Keywords:	postoperative delirium, postoperative cognitive decline, EEG guidance, quality of life, Dementia < NEUROLOGY, frailty

SCHOLARONE™
Manuscripts

1
2
3 **Title:** Ability of postoperative delirium to predict intermediate-term postoperative cognitive function in
4 patients undergoing elective surgery at an academic medical center: protocol for a prospective cohort
5 study
6

7 **Short title:** Postoperative delirium predicting intermediate-term post-operative cognitive function
8

9
10 **Protocol Authors:**

11 Amrita Aranake, MD, primary project investigator, aranakea@wustl.edu

12 Jenny Zhao Cheng, BS, j.cheng@wustl.edu

13 Maxwell Muench, BS, mrmuench@atsu.edu

14 Rose Tang, BS, tang.r@wustl.edu

15 Angela Mickle, MS, micklean@wustl.edu

16 Hannah Maybrier, BS, h.maybrier@wustl.edu

17 Nan Lin, MS, PhD, nlin@wustl.edu

18 Troy Wildes, MD, wildest@wustl.edu

19 Eric Lenze, MD, lenzee@wustl.edu

20 Michael S Avidan, MBBCh¹, avidanm@wustl.edu
21

22
23
24 **Corresponding Author:**

25
26 Michael Avidan, avidanm@wustl.edu

27 660 S Euclid Ave, Campus Box 8054

28 Saint Louis, MO 63110

29 P: 314-747-4155 F: 314-747-3977
30

31
32 **Keywords:** postoperative delirium, postoperative cognitive decline, EEG guidance, quality of life,
33 dementia, frailty
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Table of Contents

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1. Abbreviations**2. Introduction****3. Abstract****4. Background****4.1 Literature search and review****4.2 Justification****5. Specific Aims****6. Study Design****7. Study Groups****8. Recruitment****9. Data****10. Statistical Considerations****10.1 Sample size calculations****10.2 Analysis****11. Pre-specified additional analyses and sub-studies****12. Limitations****13. Compliance****13.1 Subject compliance****13.2 Withdrawal of Subjects****14. Ethical Considerations****15. Finance and insurance****16. Reporting and Dissemination****17. Author contributions****18. Acknowledgements****19. Competing interests****20. Grant information****21. References****22. Table**

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

1
2
3 Blessed Test. Multivariable regression analyses and a Cox proportional hazards analysis will be
4 performed. All results will be reported with 95% confidence intervals and $\alpha=0.05$.

5
6 **Ethics and Dissemination:** This study is approved by the ethics board at Washington University. Plans for
7 dissemination include scientific publications and presentations at scientific conferences.

8
9 **Trial registration:** This observational study is a pre-specified sub-study of ENGAGES (NCT02241655).

10 11 **Strengths and Limitations of this study:**

12 13 *Strengths:*

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

19 20 21 22 *Limitations:*

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

28 29 30 31 32 **4. Background**

33
34 Since Bedford's 1955 case series suggesting an association between surgical intervention and cognitive
35 impairment, there has been growing concern among the public that cognitive decline is a common
36 consequence of surgery.[3] This pervasive view continues to concern patients and their families, fueled
37 by anecdotal evidence and media coverage. Postoperative cognitive decline (POCD) has been a growing
38 topic for scientific investigation after several studies were published by the International Study of Post-
39 Operative Cognitive Dysfunction (ISPOCD) group. While several influential studies demonstrated early
40 postoperative cognitive decline (POCD) lasting up to 3 months, the persistence of this cognitive decline
41 has been controversial.[4-8] Importantly, the population of Americans older than 60 years is projected
42 to double over the next 30 years,[9] and many will require surgery. Acute and long-term cognitive
43 changes related to surgical intervention are particularly distressing to patients and their families.
44 Therefore, clarification of cognitive outcomes would assist patients and practitioners in making an
45 informed decision about the relative risks and benefits of proceeding with elective surgery.

46 47 48 49 **4.1 Literature search and review**

50
51 A systemized literature review was conducted with the help of a librarian experienced in systemic
52 review (see Acknowledgement). Ovid Medline was searched for studies published between 1981 and
53 September 2016 using the query: Postoperative or after surgery AND Delirium AND Cognitive function
54 or dementia AND Elderly AND Long-term or intermediate term or follow up or cohort studies or
55 retrospective studies. Articles in English or with English translation were considered. JC and RT reviewed
56 the 301 search results and found 28 articles that were relevant to our clinical question. 21 out of the 28
57
58
59
60

1
2
3 relevant articles (84%) showed significant result in the relationship between postoperative delirium
4 (POD) and intermediate- to long-term cognitive decline. These seem to suggest a high pre-test
5 probability in studying the ability of POD to predict intermediate-term cognitive decline. However, these
6 studies are heterogeneous in the study design, selected surgical patient population, and outcome
7 measurement tools complicating synthesis of the systemic search to draw conclusions.
8
9

10 POD is a common complication for surgical patients over the age of 60 years.[10] It is a neurological
11 syndrome characterized by a combination of features, which can include an acute change, fluctuating
12 course, disordered thinking, altered consciousness and inattention. Although usually transient, POD has
13 been associated with several salient adverse outcomes, including mortality, prolonged ICU stay and
14 persistent cognitive decline.[11-14] One prospective cohort study of cardiac surgery patients suggested
15 patients experiencing POD had prolonged cognitive impairment at one year.[14] However, after
16 adjusting for baseline differences in cognitive function, there was no significant difference compared
17 with controls. The same study also demonstrated that mild cognitive impairment preoperatively may
18 predispose patients to delirium; thus POD may be exposing patients who are already experiencing sub-
19 clinical cognitive decline or those who have an underlying vulnerability to cognitive decline. Another
20 study, in orthopedic surgery patients found no association between POD and cognitive decline at three
21 months.[15] There are few articles addressing the association between POD and persistent
22 postoperative cognitive decline (arbitrarily defined as lasting >6 months). A prospective matched
23 controlled survey with an average of 30-month follow-up demonstrated that dementia or mild cognitive
24 impairment was diagnosed in 77.8% of the surviving hip surgery patients with POD, almost doubling the
25 40.9% rate of control patients (relative risk = 1.9, 95% CI = 1.1-3.3). However the study was
26 underpowered to evaluate the long-term cognitive function, as the power calculation was based on the
27 original study and no intermediate assessments were made to track patients' cognitive function.[16]
28 Overall, the results of these studies suggest an association between POD and persistent cognitive
29 impairment, however compelling data supporting an independent association are lacking.
30
31
32
33

34 In addition to cognitive outcomes, quality of life and functional capacity are also important patient-
35 centered outcomes that require further investigation. While one study found that elderly surgical
36 patients tended to have long-term cognitive and functional decline compared to non-surgical
37 patients,[17] few studies have examined the association between cognitive function and quality of life
38 or activities of daily living. One prospective study over a 10-month period demonstrated that delirium
39 was an independent risk factor for becoming dependent for personal activities of daily living after ICU
40 discharge (OR = 2.188, P <0.046) and that patients with POD also demonstrated a greater decline in
41 Short-Form-36 domains after discharge, especially in physical function, vitality, and social function.[18]
42 However, this study could not draw conclusions regarding cognitive function due to lack of data.
43 Kastaun et al. reported perceived impairment in ability to perform activities of daily living one year after
44 surgery, however did not detect significant cognitive decline at that time.[19] It remains unclear
45 whether cognitive decline results in impaired functional capacity or decreased quality of life. In fact,
46 given the variable definitions of POCD, data from previous studies are difficult to interpret. As many of
47 the deficits found in neuropsychiatric testing are subtle, it is possible that detected cognitive impairment
48 has no clinically significant impact on these patient-centered outcomes. Instead of using an arbitrary
49 threshold to dichotomize cognitive function as normal or impaired, it would be more informative to
50 correlate these outcomes with cognitive function as a continuous variable or stratified into multiple
51 groups.
52
53
54

55 **4.2 Justification**

56
57
58
59
60

1
2
3 The population of older adults is projected to double over the next thirty years, and many will undergo
4 elective surgery with the hope of overall improvement in health and quality of life. Postoperative
5 delirium is a common and potentially preventable complication, thus clarification of its association with
6 persistent declines in cognition and quality of life will inform perioperative care. Prior studies have not
7 demonstrated an association independent of pre-existing patient characteristics and perioperative
8 course. The proposed study addresses the methodologic concerns in current literature by: 1. objectively
9 evaluating attention and executive function with validated cognitive tests, 2. obtaining measurements of
10 baseline cognitive function, 3. conducting statistical analysis which includes important potential
11 confounding factors including frailty measures, and 4. sampling from an unselected surgical population.
12 The results of this study will contribute to the broader understanding of postoperative cognitive
13 changes, and may help identify and provide therapies for susceptible patients earlier to ultimately
14 improve outcomes.
15
16
17

18 As part of the ENGAGES study, patients have been enrolling since January 2015, with 804 patients
19 enrolled thus far. Over the last year, the ENGAGES research team has enrolled approximately 35
20 patients per month, and has gathered baseline cognitive data on a majority of participants. Preliminary
21 screening suggests about 65% of those enrolled in ENGAGES are eligible for the current study.
22 Anticipating that half of those contacted will enroll, we expect to assess 10 to 15 patients per month.
23 The scaffold of ENGAGES and trained study members make this sub-study highly feasible.
24
25
26
27

28 **5. Specific Aims**

29
30 **Specific Aim #1:** Determine whether patients who experience postoperative delirium perform worse on
31 specific cognitive tests at approximately one year after surgery.
32

33 We hypothesize that postoperative delirium is independently associated with poorer performance on
34 tests of attention and executive function at one year after surgery. We will conduct a regression
35 analysis, including likely contributory variables, to assess the association between delirium and cognitive
36 decline at approximately one year.
37

38 **Specific Aim #2:** Evaluate whether patients who experience postoperative delirium have worse quality
39 of life at approximately one year postoperatively.
40

41 We hypothesize that postoperative delirium is independently associated with decreased quality of life
42 one year after surgery. We will conduct a regression analysis, including likely contributory variables, to
43 assess the association between delirium and health-related quality of life at approximately one year.
44
45

46 **Specific Aim #3:** Explore whether patients who experience postoperative delirium are more likely to
47 develop dementia within approximately one to two years of their surgery.
48

49 We hypothesize that postoperative delirium is independently associated with incident dementia one to
50 two years after surgery. We will conduct a Cox proportional hazards regression, including likely
51 contributory variables, to assess the rate of incident dementia approximately one to two years after
52 surgery.
53
54
55

56 **6. Study Design:**

57
58
59
60

1
2
3 This prospective cohort study is pre-specified sub-study of the ENGAGES study. The ENGAGES study is a
4 randomized clinical trial enrolling approximately 1,200 patients sixty years and older who will undergo
5 elective major surgery at Barnes Jewish Hospital (BJH), St. Louis, MO.
6

7
8 The parent trial will recruit patients primarily from the Center for Preoperative Assessment and Planning
9 (CPAP) clinic. Among inclusion criteria for ENGAGES, details of which have been previously
10 published,[20] is enrollment in the Systematic Assessment and Targeted Improvement of Services
11 Following Yearly Surgical Outcomes Surveys (SATISFY-SOS) study. As part of ENGAGES, participants will
12 complete a comprehensive baseline assessment including cognitive tests, frailty measures, and
13 screening for delirium and dementia. Postoperatively, patients will have daily evaluations for delirium
14 during the hospital stay. The current study will retrospectively identify 200 participants who reside
15 within approximately 45 miles from the hospital or those who have a planned visit to the hospital
16 between ten to sixteen months post-operatively. Patients diagnosed with delirium postoperatively will
17 be compared to those without delirium. A prospective intermediate-term postoperative assessment will
18 be conducted by a research team member blinded to whether the patient developed postoperative
19 delirium.
20
21
22
23

24 **7. Study Groups**

25
26 The target population for this study is patients who underwent preoperative assessment for elective
27 surgery at the Center for Preoperative Assessment and Planning (CPAP) clinic at Barnes Jewish Hospital
28 (BJC) in St. Louis, Missouri. The ENGAGES study is enrolling 1,232 patients who are already enrolled in
29 the SATISFY-SOS study. Inclusion criteria include patients sixty years old and older, who are competent
30 to provide informed consent and who are undergoing major elective surgery under general anesthesia
31 with a potent volatile anesthetic agent that requires a minimum stay of two days postoperatively (i.e.,
32 open cardiac surgery, open thoracic surgery, major vascular surgery, intra-abdominal surgery, open
33 gynecologic surgery, open urologic surgery, major orthopedic surgery, open hepato-biliary surgery and
34 major ear, nose and throat surgery). The ENGAGES study has minimal exclusion, as there are no absolute
35 contraindications to EEG monitoring. Exclusion criteria include neurosurgical procedures, preoperative
36 delirium, patients who are unable to participate adequately in delirium screening, including those who
37 are blind, deaf, illiterate, or not fluent in English, patients with a history of intraoperative awareness
38 during intended general anesthesia, and patients who had a second surgery planned within five days
39 after the index surgery. This prospective study will enroll 200 patients who are already enrolled in the
40 ENGAGES and SATISFY-SOS studies. In addition to previously described inclusion and exclusion criteria,
41 participants will be included in this study if their home residence is ≤ 45 miles from BJH or they have a
42 planned visit to the hospital within the specified timeframe. Patients who have not completed the
43 baseline cognitive assessment with Trails A, Trails B and the Stroop Color Word Test will also be
44 excluded from this study.
45
46
47
48
49
50

51 **8. Recruitment**

52
53 As part of the SATISFY-SOS study, patients have given informed consent to be contacted by Washington
54 University for follow-up of health-related outcomes up to a year after surgery. Eligible participants will
55 be identified by chart review and query of the ENGAGES REDCap database. A member of the research
56 team will contact potential participants by telephone approximately ten to sixteen months after surgery
57 for enrollment in this study. Patients may refuse participation in the study. If patients agree to
58
59
60

1
2
3 participation, written consent will be obtained when the patient comes in for assessment, prior to any
4 data collection. Patients will then be prospectively evaluated with assessments of cognition, quality of
5 life, and frailty measures, which are described in detail below. Meal vouchers will be provided for
6 participation. Patients residing within approximately 45 miles of the hospital, who are willing to
7 participate in the study, but unable or unwilling to come to the study center will be offered assessment
8 at home by a member of the research team. Additionally, ENGAGES patients who have not completed a
9 one-year dementia screening will be contacted by telephone approximately 18 to 24 months after
10 surgery. Phone consent will be obtained to complete dementia screening over the telephone.
11
12 Participants may refuse to participate.
13

14 15 16 17 **9. Data**

18 19 **9.1 Data Collection**

20
21 Routinely obtained baseline assessment in the CPAP clinic includes demographic information, a detailed
22 medical history, surgical history, medications and physical examination. As part of SATISFY-SOS and
23 ENGAGES, baseline assessment using the Barthel Index, Veteran's RAND 12-item Health Survey (VR-12),
24 Eight-item Interview to Differentiate Aging and Dementia (AD-8), Short Blessed Test, alcohol sniff test,
25 and Personal Health Questionnaire Depression Scale (PHQ8) will be performed. Baseline cognitive
26 function will be evaluated by the ENGAGES team with the Trails A and B, and the Stroop Color and Word
27 Test. Some patients may complete computer-based cognitive testing with the NIH toolbox at baseline
28 (described below). Additionally, frailty will be assessed using grip strength, Timed-up and Go (TUG) test,
29 and obtaining fall history at baseline. Participants will have daily delirium assessments by trained
30 researchers with the Confusion Assessment Method in the postoperative period for the duration of their
31 hospital stay. Data collected by the ENGAGES team will be entered into the Washington University
32 School of Medicine Research Electronic Data Capture (REDCap) application. [18] Perioperative data will
33 be retrieved from the hospital's perioperative electronic medical record (Metavision by iMDsoft®,
34 Needham, MA). High fidelity perioperative data is routinely captured from our EMR to an SQL server
35 (Microsoft, Redmond, WA) database. These data include bispectral index (BIS) values, EEG burst
36 suppression durations, laboratory data, intraoperative medications, physiological readings, and
37 postoperative recovery parameters. All the data for SATISFY-SOS are integrated from various data
38 sources and are stored in a single data repository housed in the Department of Anesthesiology at
39 Washington University.
40
41
42

43
44 Cognition: The primary outcome in this study will be a composite score comprised of scores from three
45 cognitive tests evaluating attention and executive function: Trails A, Trails B and Stroop Color Word Test.
46 These cognitive tests will be repeated approximately one year after surgery to evaluate intermediate
47 term cognitive function. The research team member performing the assessments will be blinded to
48 whether the patient developed postoperative delirium. In addition to the above tests, this study
49 proposes to use the Cognition Battery of the National Institutes of Health (NIH) Toolbox Assessment of
50 Neurological and Behavioral Function (<http://www.nihtoolbox.org>). The NIH Toolbox Cognition Battery
51 (Feinberg School of Medicine, Northwestern University, Chicago, IL), is a comprehensive yet concise
52 standardized computer-based assessment battery; we plan to include tasks to evaluate attention
53 (Flanker Inhibitory Control and Attention Test), episodic memory (Picture Sequence Memory Test),
54 processing speed (Pattern Comparison Processing Speed Test), language (Picture Vocabulary), and
55 executive function (Dimensional Change Card Sort Test and Flanker Inhibitory Control and Attention
56 Test). Patients will have the option of completing all of the NIH Toolbox Cognition tests above, which
57
58
59
60

1
2
3 takes approximately 25 minutes, or an abbreviated version, which takes approximately 10 minutes to
4 complete. The NIH Toolbox Cognition Battery has been validated for use across a wide range of ages.[21,
5 22] Self-reported cognitive function will be evaluated by The Patient Reported Outcomes Measurement
6 Information System (PROMIS). PROMIS, funded by the National Institutes of Health (NIH), is a set of
7 highly reliable, valid, flexible, precise, and responsive assessment tools that measure patient-reported
8 health status. PROMIS v1.0-Applied Cognition-General Concerns-Short Form 4a is comprised of four
9 questions about thinking and cognition. PROMIS v1.0-Applied Cognition-Abilities-Short Form 4a is
10 comprised of four questions about memory. Evaluation for dementia with the Short Blessed Test will be
11 completed for all patients at baseline, and again between one to two years after surgery.
12
13

14
15 Quality of Life: As part of the ongoing SATISFY-SOS study, patient self-reported Health-related Quality of
16 Life information will be assessed through the VR-12 at baseline (preoperatively) and also one year after
17 surgery. The VR-12 was derived from the Veterans RAND 36 Item Health Survey (VR-36) and contains
18 twelve items relating to quality of life, including physical and mental health, as well as specific questions
19 about functional status. Physical and Mental Health Summary Scores will be calculated. The VR-12 has
20 been validated and is widely applied as a metric for tracking health-related quality of life in the United
21 States.[23]
22

23
24 Functional status: We will assess functional status with the Barthel Index for Activities of Daily Living and
25 Lawton Instrumental Activities of Daily Living Scale. The Barthel Index is a measure of patient
26 performance in ten activities comprised of eight questions about personal care and two questions about
27 mobility. The Lawton Scale assesses independent living skills in 8 areas of function.
28

29
30 Frailty: We will measure grip strength and the Timed Up and Go (TUG) test. Grip strength will also be
31 assessed with three measurements in the dominant hand using a Jamar® handheld dynamometer
32 (Lafayette Instruments, Lafayette, IN). Maximal grip strength will be selected for analysis.
33

34 **9.2 Data management**

35
36 A customized database has been developed to facilitate data management for this study using the
37 Research Electronic Data Capture (REDCap) system. REDCap is a secure web-based data capture system
38 available to research groups receiving support from the Institute of Clinical and Translational Sciences at
39 Washington University. It is maintained by the Washington University Division of Biostatistics with
40 multiple capabilities to simplify data management and analysis. These include intuitive data entry, data
41 audit and tracking, import of externally sourced data, and automated data export for analysis. REDCap
42 requires unique user identification and password combinations for secure access.
43
44

45 **10. Statistical Consideration**

46 **10.1 Sample calculations**

47
48 For specific aims 1&2, continuous outcome variables will be evaluated using multivariable methods. To
49 have a robust predictive model and prevent overfitting, it is necessary to have at least ten observations
50 for each parameter included in the model. We plan to include ten to twelve parameters in the
51 regression models for aims 1&2, which are specified further below. To ensure an adequate number of
52 observations and avoid overfitting, we plan to enroll 200 patients in this study.
53
54
55
56
57
58
59
60

1
2
3 For specific aim 3, sample size calculation has been performed using G*POWER 3.0.10. Based on results
4 of a previously published meta-analysis of four studies investigating the use of BIS-guided anesthetic
5 administration, we conservatively assume an incidence of POD of 25%. For patients without delirium, we
6 expect the rate of incident dementia to be 5%. To detect two-fold increase in the rate of dementia, with
7 a one sided alpha <5%, unequal cohorts, and 80% power, the study would need 861 participants (215 in
8 the delirium group, and 646 in the control group).
9
10

11 **10.2 Statistical analysis**

12
13 We will perform and report descriptive statistics (mean and standard deviation) for all variables
14 between patients with and without the diagnosis of POD. Descriptive statistics will include chi-squared
15 tests for categorical variables, t-tests for normally distributed continuous variables and Mann-Whitney
16 tests for nonparametric continuous variables.
17

18
19 Specific Aim 1: Determine whether patients who experience POD perform worse on specific cognitive
20 tests at approximately one year after surgery.
21

22 The primary endpoint of our analysis is cognitive function one year after surgery, as measured by the
23 Trails A & B and the Stroop Color Word Test. Z-scores will be calculated for performance for each test,
24 and combined to form a composite measure. Multivariable regression analysis will be used to determine
25 whether the development of postoperative delirium is a predictor variable for cognitive function,
26 independent from other possible contributory factors. POD will be entered as discrete numerical
27 variable reflecting duration of symptoms. The following variables will be included in the model: age, sex,
28 American Society of Anesthesiologists physical score, and Charlson co-morbidity index. The following
29 known or suggested risk factors cognitive decline will also be included in the model: baseline cognitive
30 function, education level, type of surgery, preoperative depression, preoperative vascular disease,
31 postoperative complications, composite score on frailty tests and a history of falls. We will use a model
32 with backward elimination, to avoid exclusion of predictors with suppressor effects.
33
34

35 Specific Aim 2: Evaluate whether patients who experience POD have worse quality of life at
36 approximately one year postoperatively.
37

38 The primary endpoint of our analysis is quality of life one year after surgery, as measured by the change
39 in VR-12 score between preoperative and postoperative assessments. Again, a multivariable regression
40 analysis will be performed to evaluate whether the development of postoperative delirium is an
41 independent predictor variable for the change in quality of life. The following variables will be included
42 in the model: age, sex, American Society of Anesthesiologists physical score, Charlson co-morbidity
43 index, type of surgery, preoperative depression, preoperative vascular disease, postoperative
44 complications, composite score on frailty tests and a history of falls. As above, we will use a model with
45 backward elimination, to avoid exclusion of predictors with suppressor effects.
46
47

48 For the above aims, we expect this study to be limited by loss to follow-up, estimated to be 50%. Those
49 lost to follow-up are likely to have more severe disease or deterioration in health. In order to determine
50 the influence of missing data in our analysis, we will also conduct a sensitivity analysis. We will calculate
51 the average cognition scores of those who declined. We will repeat the above models including missing
52 subjects, assuming all patients who did not participate had cognitive decline, quantified by the average
53 calculated from participants above.
54
55

56 Specific Aim 3: Explore whether patients who experience POD are more likely to become demented
57 within approximately one to two years of their surgery.
58
59
60

1
2
3 The primary endpoint of our analysis is incident dementia. A Cox proportional hazards regression will be
4 used to explore the likelihood of incident dementia associated with POD. The following variables will be
5 included in the model: age, sex, American Society of Anesthesiologists physical score, Charlson co-
6 morbidity index, preoperative cognitive function, type of surgery, preoperative depression, preoperative
7 vascular disease, postoperative complications, and composite score on frailty tests and a history of falls.
8
9

10 All statistical analyses will be performed using SAS, version 9.4 (SAS Institute, Inc., Cary, North Carolina).
11 To determine whether postoperative delirium increases risk of incident dementia, the Cox proportional
12 hazards model will be one-sided. All other tests will be two-sided. By arbitrary convention all tests will
13 be considered statistically significant at a $p < 0.05$, and all results will be presented with estimates and
14 95% confidence intervals.
15

16 **11. Pre-specified additional analyses and sub-studies**

17
18 The primary aim of this study is to determine whether postoperative delirium predicts intermediate-
19 term cognitive impairment. However, as a sub-study of ENGAGES and SATISFY-SOS, several other
20 clinically relevant outcomes can be explored as well. SATISFY-SOS systematically collects detailed
21 information regarding patient centered outcomes, including patient perceived cognition. Correlation
22 between performance on neurocognitive testing and patient perceived cognition would be interesting
23 and useful clinically. Furthermore, the information regarding patients' characteristics will allow
24 exploration of risk factors for intermediate-term cognitive impairment. Lastly, as part of ENGAGES, some
25 patients will have baseline NIH Toolbox cognitive testing, allowing description of long-term cognitive
26 trajectories as evaluated by these tests.
27
28

29 **12. Limitations**

30
31 This study contains several limitations. First, of most concern is the potential for non-response bias if
32 patients who do not participate are not a random subset of those contacted. We will attempt to
33 minimize the non-response rate by offering to visit patients at their homes if patients are unwilling to
34 come to the study center. We expect that those lost to follow-up would be more likely to have more
35 severe disease or health deterioration, potentially affecting cognitive function. We will thus conduct
36 appropriate sensitivity analyses to determine how missing outcomes data could alter the findings of our
37 study. Second, with an observational study, we cannot establish a causal relationship between
38 postoperative delirium and persistent declines in cognitive and quality of life. If an independent
39 relationship is found, we shall not be able to disambiguate whether postoperative delirium in some way
40 causes persistent decline in these outcomes, or whether it is a sign of underlying vulnerability. However,
41 since it is not possible to randomize patients to experience delirium, this limitation might be inevitable.
42 Third, since patients in this study are recruited from a single tertiary care center, the study sample may
43 not be representative of surgical patients in general. While these patients tend to have higher comorbid
44 disease burden than the general surgical population, including comorbidities in the statistical model will
45 account for these differences. Finally, while we have baseline cognitive assessments, we do not have
46 preoperative cognitive trajectories, and thus cannot determine whether the results of cognitive function
47 tests are a deviation from the pre-operative trend.
48
49
50
51
52
53

54 **13. Compliance**

55 **13.1 Subject Compliance**

56
57
58
59
60

1
2
3 The exposure of this study is post-operative delirium, so no monitoring of exposure compliance is
4 necessary. Methods to improve completion of one-year cognitive testing are described in Section 10.3,
5 "Limitations."
6

7 8 **13.2 Withdrawal of subjects**

9
10 Subjects may be withdrawn from the study only if requested by the patient. The reason for withdrawal
11 is recorded by the team's clinical project specialist.
12

13 14 15 **14. Ethical Considerations**

16
17 This study has been approved by the home institution's Institutional Review Board (IRB ID # 201407128).
18 Written, informed consent is obtained from all participants. As described in Section 7, "Study Groups,"
19 no special allowances are made for patients who are blind, deaf, illiterate or not fluent in English.
20 Participants may withdraw from the study at any time.
21

22 23 24 **15. Finance and Insurance**

25
26 Since this study involves only cognitive testing and surveys, it involves no more than minimal risk to the
27 patients. Finance details, insurance details, and cover for negligent and non-negligent harm are
28 therefore not relevant in this study.
29

30 31 32 **16. Reporting and Dissemination**

33
34 Results of this study will be published in a scientific journal. Participants will only be notified individually
35 if discoveries are made that directly impact their health.
36

37 38 39 **17. Author Contributions**

40
41 Authorship for this study will be given to key personnel involved in study design, recruitment, data
42 collection and data analysis. There are no publication restrictions, and no professional writers will be
43 involved in the generation of the manuscript. MSA, AA, JZC, MM, RT, TW, EL are responsible for
44 conceptualizing study design. AA, JZC, RT, MM, HM, and AM were responsible for recruitment,
45 enrollment, data collection and editing the protocol. AA, JZC, and RT are responsible for drafting the
46 protocol. All authors including AA, JZC, MM, RT, AM, HM, NL, TW, EL, and MSA have critically revised the
47 protocol and approved the final version.
48
49

50 51 52 **18. Acknowledgement**

53
54 We thank Ms. Michelle Doering, a medical librarian at Becker Medical Library at Washington University
55 School of Medicine for developing the systemic search criteria.
56
57
58
59
60

19. Competing Interests

The authors and contributors have no competing interests to disclose.

20. Grant Information

Funding for this study was awarded by the Foundation for Anesthesia Education and Research (award reference ID RFG-08/15/2016-Aranake-Chrisinger). Funding for the ENGAGES trial was through a UH2/UH3 mechanism grant awarded by the National Institute on Aging (1UH2AG050312-01). Funding for the SATISFY-SOS study was from a grant awarded by the Barnes-Jewish Hospital Foundation (7937-77) and support provided by the Department of Anesthesiology at Washington University.

21. References

1. von Elm, E., et al., *The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies*. *Int J Surg*, 2014. **12**(12): p. 1495-9.
2. Biostatistics Group, U.U.R.B.R.U. *Guidelines for Completing a Research Protocol for Observational Studies*. 9 April 2010 [cited 2017 January 4]; Available from: https://www.ucl.ac.uk/jro/biostatistics/obs_protocol_guidelines.pdf.
3. Bedford, P.D., *Adverse cerebral effects of anaesthesia on old people*. *Lancet*, 1955. **269**(6884): p. 259-63.
4. Moller, J.T., et al., *Long-term postoperative cognitive dysfunction in the elderly ISPOCD1 study. ISPOCD investigators. International Study of Post-Operative Cognitive Dysfunction*. *Lancet*, 1998. **351**(9106): p. 857-61.
5. Monk, T.G., et al., *Predictors of cognitive dysfunction after major noncardiac surgery*. *Anesthesiology*, 2008. **108**(1): p. 18-30.
6. Selnes, O.A., et al., *Cognition 6 years after surgical or medical therapy for coronary artery disease*. *Ann Neurol*, 2008. **63**(5): p. 581-90.
7. Avidan, M.S., et al., *Long-term cognitive decline in older subjects was not attributable to noncardiac surgery or major illness*. *Anesthesiology*, 2009. **111**(5): p. 964-70.
8. Dokkedal, U., et al., *Cognitive Functioning after Surgery in Middle-aged and Elderly Danish Twins*. *Anesthesiology*, 2016. **124**(2): p. 312-21.
9. *Projected Future Growth of the Older Population*. [cited 2016 02/22]; Available from: http://www.aoa.gov/AoARoot/Aging_Statistics/future_growth/future_growth.aspx - age.
10. Whitlock, E.L., A. Vannucci, and M.S. Avidan, *Postoperative delirium*. *Minerva Anestesiol*, 2011. **77**(4): p. 448-56.
11. Gottesman, R.F., et al., *Delirium after coronary artery bypass graft surgery and late mortality*. *Ann Neurol*, 2010. **67**(3): p. 338-44.
12. Koster, S., et al., *Consequences of delirium after cardiac operations*. *Ann Thorac Surg*, 2012. **93**(3): p. 705-11.
13. Bickel, H., et al., *High risk of cognitive and functional decline after postoperative delirium. A three-year prospective study*. *Dement Geriatr Cogn Disord*, 2008. **26**(1): p. 26-31.
14. Saczynski, J.S., et al., *Cognitive trajectories after postoperative delirium*. *N Engl J Med*, 2012. **367**(1): p. 30-9.
15. Jankowski, C.J., et al., *Cognitive and functional predictors and sequelae of postoperative delirium in elderly patients undergoing elective joint arthroplasty*. *Anesth Analg*, 2011. **112**(5): p. 1186-93.
16. Kat, M.G., et al., *Long-term cognitive outcome of delirium in elderly hip surgery patients. A prospective matched controlled study over two and a half years*. *Dement Geriatr Cogn Disord*, 2008. **26**(1): p. 1-8.
17. Schenning, K.J., et al., *Surgery is associated with ventricular enlargement as well as cognitive and functional decline*. *Alzheimers Dement*, 2015.
18. Abelha, F.J., et al., *Outcome and quality of life in patients with postoperative delirium during an ICU stay following major surgery*. *Crit Care*, 2013. **17**(5): p. R257.
19. Kastaun, S., et al., *The Relevance of Postoperative Cognitive Decline in Daily Living: Results of a 1-Year Follow-up*. *J Cardiothorac Vasc Anesth*, 2016. **30**(2): p. 297-303.
20. Wildes, T.S., et al., *Protocol for the Electroencephalography Guidance of Anesthesia to Alleviate Geriatric Syndromes (ENGAGES) study: a pragmatic, randomised clinical trial*. *BMJ Open*, 2016. **6**(6): p. e011505.

- 1
 - 2
 - 3
 - 4
 - 5
 - 6
 - 7
 - 8
 - 9
 - 10
 - 11
 - 12
 - 13
 - 14
 - 15
 - 16
 - 17
 - 18
 - 19
 - 20
 - 21
 - 22
 - 23
 - 24
 - 25
 - 26
 - 27
 - 28
 - 29
 - 30
 - 31
 - 32
 - 33
 - 34
 - 35
 - 36
 - 37
 - 38
 - 39
 - 40
 - 41
 - 42
 - 43
 - 44
 - 45
 - 46
 - 47
 - 48
 - 49
 - 50
 - 51
 - 52
 - 53
 - 54
 - 55
 - 56
 - 57
 - 58
 - 59
 - 60
21. Bleck, T.P., et al., *What is the NIH toolbox, and what will it mean to neurology?* *Neurology*, 2013. **80**(10): p. 874-5.
22. Weintraub, S., et al., *Cognition assessment using the NIH Toolbox*. *Neurology*, 2013. **80**(11 Suppl 3): p. S54-64.
23. Selim, A.J., et al., *Updated U.S. population standard for the Veterans RAND 12-item Health Survey (VR-12)*. *Qual Life Res*, 2009. **18**(1): p. 43-52.

For peer review only

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

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

--	--	--	--	--	--

For peer review only

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 (b) Provide in the abstract an informative and balanced summary of what was done and what was found	1 and 3
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) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —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 <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants (b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case	7-8 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 (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	10 10 10-11

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

(e) Describe any sensitivity analyses

Continued on next page

For peer review only

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 (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	N/A
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time <i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure <i>Cross-sectional study</i> —Report numbers of outcome events or summary measures	N/A
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 (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	N/A
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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2017-017079.R1
Article Type:	Protocol
Date Submitted by the Author:	02-Aug-2017
Complete List of Authors:	Aranake-Chrisinger, Amrita; Washington University in Saint Louis School of Medicine, Anesthesiology Cheng, Jenny; Washington University in Saint Louis School of Medicine, Anesthesiology Muench, Maxwell; Washington University in Saint Louis School of Medicine, Anesthesiology; Kirksville College of Osteopathic Medicine, Tang, Rose; Washington University in Saint Louis School of Medicine, Anesthesiology Mickle, Angela; Washington University in Saint Louis School of Medicine, Anesthesiology Maybrier, Hannah; Washington University in Saint Louis School of Medicine, Anesthesiology Lin, Nan; Washington University in Saint Louis, Mathematics; Division of Biostatistics Wildes, Troy; Washington University in Saint Louis School of Medicine, Anesthesiology Lenze, Eric Avidan, Michael; Washington University School of Medicine, Anesthesiology
Primary Subject Heading:	Anaesthesia
Secondary Subject Heading:	Geriatric medicine, Neurology
Keywords:	postoperative delirium, postoperative cognitive decline, EEG guidance, quality of life, Dementia < NEUROLOGY, frailty

SCHOLARONE™
Manuscripts

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

Protocol Authors:

Amrita Aranake, MD, primary project investigator, aranakea@wustl.edu

Jenny Zhao Cheng, BS, j.cheng@wustl.edu

Maxwell Muench, BS, mrmuench@atsu.edu

Rose Tang, BS, tang.r@wustl.edu

Angela Mickle, MS, micklean@wustl.edu

Hannah Maybrier, BS, h.maybrier@wustl.edu

Nan Lin, MS, PhD, nlin@wustl.edu

Troy Wildes, MD, wildest@wustl.edu

Eric Lenze, MD, lenzee@wustl.edu

Michael S Avidan, MBBCh¹, avidanm@wustl.edu

Corresponding Author:

Michael Avidan, avidanm@wustl.edu

660 S Euclid Ave, Campus Box 8054

Saint Louis, MO 63110

P: 314-747-4155 F: 314-747-3977

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 $\alpha=0.05$.

1
2
3 **Ethics and Dissemination:** The study has been approved by the Washington University in St. Louis
4 Institutional Review Board (IRB #201601099). Plans for dissemination include scientific publications and
5 presentations at scientific conferences.
6

7 **Trial registration:** This is a pre-specified sub-study of ENGAGES (NCT02241655).
8

9 **Strengths and Limitations of this study:**

10 *Strengths:*

- 11 • Postoperative intermediate term cognitive function and quality of life are important patient-
- 12 centered outcomes.
- 13 • Analysis will include salient patient characteristics, including preoperative cognition, comorbid
- 14 conditions and frailty.
- 15 • Study sample will consist of an understudied population in clinical research.
- 16
- 17
- 18
- 19
- 20

21 *Limitations:*

- 22 • Potential for loss to follow-up and non-response bias
- 23 • Since this is an observational study, we cannot establish a causal relationship between
- 24 postoperative delirium and persistent declines in cognition and quality of life.
- 25 • We cannot determine whether cognitive function deviates from the pre-operative trend,
- 26 without multiple preoperative cognitive assessments to establish a trajectory.
- 27
- 28
- 29
- 30

31 **Background**

32
33 Since Bedford's 1955 case series suggesting an association between surgical intervention and cognitive
34 impairment, there has been growing concern among the public that cognitive decline is a common
35 consequence of surgery.[1] This pervasive view continues to concern patients and their families, fueled
36 by anecdotal evidence and media coverage. Postoperative cognitive decline (POCD) has been a growing
37 topic for scientific investigation after several studies were published by the International Study of Post-
38 Operative Cognitive Dysfunction (ISPOCD) group. While several influential studies demonstrated early
39 postoperative cognitive decline (POCD) lasting up to 3 months, the persistence of this cognitive decline
40 has been controversial.[2-6] Importantly, the population of Americans older than 60 years is projected
41 to double over the next 30 years,[7] and many will require surgery. Acute and long-term cognitive
42 changes related to surgical intervention are particularly distressing to patients and their families.
43 Therefore, clarification of cognitive outcomes would assist patients and practitioners in making an
44 informed decision about the relative risks and benefits of proceeding with elective surgery.
45
46
47

48 **Literature search and review**

49
50 A systemized literature review was conducted with the help of a librarian experienced in systemic
51 review (see Acknowledgement). Ovid Medline was searched for studies published between 1981 and
52 September 2016 using the query: Postoperative or after surgery AND Delirium AND Cognitive function
53 or dementia AND Elderly AND Long-term or intermediate term or follow up or cohort studies or
54 retrospective studies. Articles in English or with English translation were considered. JC and RT reviewed
55 the 301 search results and found 28 articles that were relevant to our clinical question. 21 out of the 28
56 relevant articles (75%) showed significant result in the relationship between postoperative delirium
57
58
59
60

1
2
3 (POD) and intermediate- to long-term cognitive decline (Appendix A). These seem to suggest a high pre-
4 test probability in studying the ability of POD to predict intermediate-term cognitive decline. However,
5 these studies are heterogeneous in the study design, selected surgical patient population, and outcome
6 measurement tools complicating synthesis of the systemic search to draw conclusions.
7

8
9 POD is a common complication for surgical patients over the age of 60 years.[8] It is a neurological
10 syndrome characterized by a combination of features, which must include an acute change, fluctuating
11 course, inattention, and may also include disordered thinking or altered consciousness. Although usually
12 transient, POD has been associated with several salient adverse outcomes, including mortality,
13 prolonged ICU stay and persistent cognitive decline.[9-12] One prospective cohort study of cardiac
14 surgery patients suggested patients experiencing POD had prolonged cognitive impairment at one year,
15 and those with longer duration of delirium had slower recovery.[12] However, after adjusting for
16 baseline differences in cognitive function, there was no significant difference compared with controls.
17 The same study also demonstrated that mild cognitive impairment preoperatively may predispose
18 patients to delirium; thus POD may be exposing patients who are already experiencing sub-clinical
19 cognitive decline or those who have an underlying vulnerability to cognitive decline. Another study, in
20 orthopedic surgery patients found no association between POD and cognitive decline at three
21 months.[13] While several studies have suggested that postoperative cognitive decline can persist past
22 six months after surgery,[2, 14] others have demonstrated a transient early decline with later
23 recovery.[4, 5] Furthermore, there is conflicting evidence regarding the long-term cognitive trajectories
24 of postoperative patients, with some suggesting overall improvement and others suggesting overall
25 decline.[15, 16] POD has been posited as a risk factor for lasting decline; however, few articles have
26 addressed the association between POD and persistent postoperative cognitive decline (arbitrarily
27 defined as lasting >6 months). A prospective matched controlled survey with an average of 30-month
28 follow-up demonstrated that dementia or mild cognitive impairment was diagnosed in 77.8% of the
29 surviving hip surgery patients with POD, almost doubling the 40.9% rate of control patients (relative risk
30 = 1.9, 95% CI = 1.1-3.3). However the study was underpowered to evaluate the long-term cognitive
31 function, as the power calculation was based on the original study and no intermediate assessments
32 were made to track patients' cognitive function.[17] Another prospective cohort study followed patients
33 over 36 months and found that patients with POD initially had cognitive decline with a transient
34 recovery, but then exhibited an accelerated pace of long-term cognitive decline when compared to
35 controls.[18] Overall, the results of these studies suggest an association between POD and persistent
36 cognitive impairment, however compelling data supporting an independent association are lacking.
37 Many of these studies also do not consider the duration of delirium, which may portend long-term
38 cognitive decline.[19, 20]
39
40
41
42
43

44 Pre-existing dementia or cognitive impairment is a known risk factor for POD,[8] and several studies
45 suggest an association between POD and dementia. One study in elderly orthopedic surgery patients
46 reported a relative risk of dementia in patient with POD of 10.5 compared to those without POD.[21] A
47 recent study demonstrated a similar association in elderly cardiac surgery patients.[22] However it
48 remains unclear whether POD causes, accelerates, or signifies an underlying vulnerability to cognitive
49 impairment, thus further investigation is warranted.
50
51

52 In addition to cognitive outcomes, quality of life and functional capacity are also important patient-
53 centered outcomes that require further investigation. While one study found that elderly surgical
54 patients tended to have long-term cognitive and functional decline compared to non-surgical
55 patients,[23] few studies have examined the association between cognitive function and quality of life
56 or activities of daily living. One prospective study over a 10-month period demonstrated that delirium
57 was an independent risk factor for becoming dependent for personal activities of daily living after ICU
58
59
60

1
2
3 discharge (OR = 2.188, P <0.046) and that patients with POD also demonstrated a greater decline in
4 Short-Form-36 domains after discharge, especially in physical function, vitality, and social function.[24]
5 However, this study could not draw conclusions regarding cognitive function due to lack of data.
6 Kastaun et al. reported perceived impairment in ability to perform activities of daily living one year after
7 surgery, however did not detect significant cognitive decline at that time.[25] It remains unclear
8 whether cognitive decline results in impaired functional capacity or decreased quality of life. In fact,
9 given the variable definitions of POCD, data from previous studies are difficult to interpret. As many of
10 the deficits found in neuropsychiatric testing are subtle, it is possible that detected cognitive impairment
11 has no clinically significant impact on these patient-centered outcomes. Instead of using an arbitrary
12 threshold to dichotomize cognitive function as normal or impaired, it would be more informative to
13 correlate these outcomes with cognitive function as a continuous variable or stratified into multiple
14 groups.
15
16

17
18 At our institution, patient reported postoperative outcomes are gathered as part of the Systematic
19 Assessment and Targeted Improvement of Services Following Yearlong Surgical Outcomes Surveys
20 (SATISFY-SOS) initiative (NCT02032030). Additionally, the ongoing randomized controlled trial:
21 Electroencephalography (EEG) Guidance of Anesthesia to Alleviate Geriatric syndromes (ENGAGES)
22 study, is evaluating patients for postoperative delirium.[26] Using the scaffold provided by these studies,
23 we aim to identify whether delirium is an independent predictor for intermediate-term cognitive
24 function and quality of life.
25
26

27 **Justification**

28
29 The population of older adults is projected to double over the next thirty years, and many will undergo
30 elective surgery with the hope of overall improvement in health and quality of life. Postoperative
31 delirium is a common and potentially preventable complication, thus clarification of its association with
32 persistent declines in cognition and quality of life will inform perioperative care. Prior studies have not
33 demonstrated an association independent of pre-existing patient characteristics and perioperative
34 course. The proposed study addresses the methodologic concerns in current literature by: 1. objectively
35 evaluating attention and executive function with validated cognitive tests, 2. obtaining measurements of
36 baseline cognitive function, 3. conducting statistical analysis which includes important potential
37 confounding factors including frailty measures, and 4. sampling from an unselected surgical population.
38 Given that delirium is predominantly a disorder of attention and executive function, we will focus our
39 investigation on these cognitive domains. The results of this study will contribute to the broader
40 understanding of postoperative cognitive changes, and may help identify and provide therapies for
41 susceptible patients earlier to ultimately improve outcomes.
42
43
44

45 As part of the ENGAGES study, patients have been enrolling since January 2015, with 804 patients
46 enrolled thus far. Over the last year, the ENGAGES research team has enrolled approximately 35
47 patients per month, and has gathered baseline cognitive data on a majority of participants. Preliminary
48 screening suggests about 65% of those enrolled in ENGAGES are eligible for the current study.
49 Anticipating that half of those contacted will enroll, we expect to assess 10 to 15 patients per month.
50 The scaffold of ENGAGES and trained study members make this sub-study highly feasible.
51
52
53

54 **Specific Aims**

55
56 **Specific Aim #1:** Determine whether the incidence and duration of postoperative delirium predict worse
57 performance on specific cognitive tests at approximately one year after surgery.
58
59
60

1
2
3 We hypothesize that postoperative delirium is independently associated with poorer performance on
4 tests of attention and executive function at one year after surgery, and that patients with a longer
5 duration of delirium will have more marked cognitive decrement. We will conduct a regression analysis,
6 including likely contributory variables, to assess the association between delirium and cognitive decline
7 at approximately one year.
8
9

10 **Specific Aim #2:** Evaluate whether the incidence and duration of postoperative delirium predict worse
11 quality of life at approximately one year postoperatively.
12

13 We hypothesize that postoperative delirium is independently associated with decreased quality of life
14 one year after surgery, and that patients with a longer duration of delirium will have more marked
15 decrease in health-related quality of life. We will conduct a regression analysis, including likely
16 contributory variables, to assess the association between delirium and health-related quality of life at
17 approximately one year.
18
19

20 **Specific Aim #3:** Explore whether patients who experience postoperative delirium are more likely to
21 develop dementia within approximately one to two years of their surgery.
22

23 We hypothesize that postoperative delirium is independently associated with incident dementia one to
24 two years after surgery. We will conduct a Cox proportional hazards regression, including likely
25 contributory variables, to assess the rate of incident dementia approximately one to two years after
26 surgery.
27
28
29

30 **Study Design:**

31
32 This prospective cohort study is pre-specified sub-study of the ENGAGES study. The ENGAGES study is a
33 randomized clinical trial enrolling approximately 1,200 patients sixty years and older who will undergo
34 elective major surgery at Barnes Jewish Hospital (BJH), St. Louis, MO.
35
36

37 The parent trial will recruit patients primarily from the Center for Preoperative Assessment and Planning
38 (CPAP) clinic. Among inclusion criteria for ENGAGES, details of which have been previously
39 published,[26] is enrollment in the SATISFY-SOS study.[27] As part of ENGAGES, participants will
40 complete a comprehensive baseline assessment including cognitive tests, frailty measures, and
41 screening for delirium and dementia. Postoperatively, patients will have daily evaluations for delirium
42 during the hospital stay. The current study will retrospectively identify 130 participants who reside
43 within approximately 45 miles from the hospital or those who have a planned visit to the hospital
44 between ten to sixteen months post-operatively. Patients diagnosed with delirium postoperatively will
45 be compared to those without delirium. A prospective intermediate-term postoperative assessment will
46 be conducted by a research team member blinded to whether the patient developed postoperative
47 delirium.
48
49

50 **Study Groups**

51
52 The target population for this study is patients who underwent preoperative assessment for elective
53 surgery at the Center for Preoperative Assessment and Planning (CPAP) clinic at Barnes Jewish Hospital
54 (BJC) in St. Louis, Missouri. The ENGAGES study is enrolling 1,232 patients who are already enrolled in
55 the STATISFY-SOS study. Inclusion criteria include patients sixty years old and older, who are competent
56
57
58
59
60

1
2
3 to provide informed consent and who are undergoing major elective surgery under general anesthesia
4 with a potent volatile anesthetic agent that requires a minimum stay of two days postoperatively (i.e.,
5 open cardiac surgery, open thoracic surgery, major vascular surgery, intra-abdominal surgery, open
6 gynecologic surgery, open urologic surgery, major orthopedic surgery, open hepato-biliary surgery and
7 major ear, nose and throat surgery). The ENGAGES study has minimal exclusion, as there are no absolute
8 contraindications to EEG monitoring. Exclusion criteria include neurosurgical procedures, preoperative
9 delirium, patients who are unable to participate adequately in delirium screening, including those who
10 are blind, deaf, illiterate, or not fluent in English, patients with a history of intraoperative awareness
11 during intended general anesthesia, and patients who had a second surgery planned within five days
12 after the index surgery. This prospective study will enroll 130 patients who are already enrolled in the
13 ENGAGES and SATISFY-SOS studies (Appendix B). In addition to previously described inclusion and
14 exclusion criteria, participants will be included in this study if their home residence is ≤ 45 miles from BJH
15 or they have a planned visit to the hospital within the specified timeframe. Patients who have not
16 completed the baseline cognitive assessment with Trails A, Trails B and the Stroop Color Word Test will
17 also be excluded from this study.
18
19
20
21
22

23 Recruitment

24
25 As part of the SATISFY-SOS study, patients have given informed consent to be contacted by Washington
26 University for follow-up of health-related outcomes up to a year after surgery. Eligible participants will
27 be identified by chart review and query of the ENGAGES REDCap database. A member of the research
28 team will contact potential participants by telephone approximately ten to sixteen months after surgery
29 for enrollment in this study. Patients may refuse participation in the study. If patients agree to
30 participation, written consent will be obtained when the patient comes in for assessment, prior to any
31 data collection. Patients will then be prospectively evaluated with assessments of cognition, quality of
32 life, and frailty measures, which are described in detail below. Meal vouchers will be provided for
33 participation. Patients residing within approximately 45 miles of the hospital, who are willing to
34 participate in the study, but unable or unwilling to come to the study center will be offered assessment
35 at home by a member of the research team. Additionally, ENGAGES patients who have not completed a
36 one-year dementia screening will be contacted by telephone approximately 18 to 24 months after
37 surgery. Phone consent will be obtained to complete dementia screening over the telephone.
38 Participants may refuse to participate.
39
40
41
42
43

44 Data

45 Data Collection

46
47
48 Routinely obtained baseline assessment in the CPAP clinic includes demographic information, a detailed
49 medical history, surgical history, medications and physical examination. As part of SATISFY-SOS and
50 ENGAGES, baseline assessment using the Barthel Index, Veteran's RAND 12-item Health Survey (VR-12),
51 Eight-item Interview to Differentiate Aging and Dementia (AD-8), Short Blessed Test (SBT), alcohol sniff
52 test, and Personal Health Questionnaire Depression Scale (PHQ8) will be performed. Baseline cognitive
53 function will be evaluated by the ENGAGES team with the Trails A and B, and the Stroop Color and Word
54 Test. Some patients may complete computer-based cognitive testing with the NIH toolbox at baseline
55 (described below). Additionally, frailty will be assessed using grip strength, Timed-up and Go (TUG) test,
56 and obtaining fall history at baseline. Participants will have daily delirium assessments by trained
57
58
59
60

1
2
3 researchers with the Confusion Assessment Method in the postoperative period for the duration of their
4 hospital stay. Data collected by the ENGAGES team will be entered into the Washington University
5 School of Medicine Research Electronic Data Capture (REDCap) application. [18] Perioperative data will
6 be retrieved from the hospital's perioperative electronic medical record (Metavision by iMDsoft®,
7 Needham, MA). High fidelity perioperative data is routinely captured from our EMR to an SQL server
8 (Microsoft, Redmond, WA) database. These data include bispectral index (BIS) values, EEG burst
9 suppression durations, laboratory data, intraoperative medications, physiological readings, and
10 postoperative recovery parameters. All the data for SATISFY-SOS are integrated from various data
11 sources and are stored in a single data repository housed in the Department of Anesthesiology at
12 Washington University.
13
14

15
16 Cognition: The primary outcome in this study will be a composite score comprised of scores from three
17 cognitive tests evaluating attention and executive function: Trails A, Trails B and Stroop Color Word Test.
18 These cognitive tests will be repeated approximately one year after surgery to evaluate intermediate
19 term cognitive function. The research team member performing the assessments will be blinded to
20 whether the patient developed postoperative delirium. In addition to the above tests, this study
21 proposes to use the Cognition Battery of the National Institutes of Health (NIH) Toolbox Assessment of
22 Neurological and Behavioral Function (<http://www.nihtoolbox.org>). The NIH Toolbox Cognition Battery
23 (Feinberg School of Medicine, Northwestern University, Chicago, IL), is a comprehensive yet concise
24 standardized computer-based assessment battery; we plan to include tasks to evaluate attention
25 (Flanker Inhibitory Control and Attention Test), episodic memory (Picture Sequence Memory Test), and
26 executive function (Dimensional Change Card Sort Test and Flanker Inhibitory Control and Attention
27 Test). Patients will complete the NIH Toolbox Cognition tests above, which takes approximately 10
28 minutes to complete. The NIH Toolbox Cognition Battery has been validated for use across a wide range
29 of ages.[28, 29] Self-reported cognitive function will be evaluated by The Patient Reported Outcomes
30 Measurement Information System (PROMIS). PROMIS, funded by the National Institutes of Health (NIH),
31 is a set of highly reliable, valid, flexible, precise, and responsive assessment tools that measure patient-
32 reported health status. PROMIS v1.0-Applied Cognition-General Concerns-Short Form 4a is comprised of
33 four questions about thinking and cognition. PROMIS v1.0-Applied Cognition-Abilities-Short Form 4a is
34 comprised of four questions about memory. Evaluation for dementia with the SBT will be completed for
35 all patients at baseline, and again between one to two years after surgery. The SBT has been shown to
36 have 95% sensitivity for detecting cognitive dysfunction when compared with the MMSE, and can be
37 administered in approximately 3 minutes, making it an excellent screening tool.[30]
38
39
40
41

42 Quality of Life: As part of the ongoing SATISFY-SOS study, patient self-reported Health-related Quality of
43 Life information will be assessed through the VR-12 at baseline (preoperatively) and also one year after
44 surgery. The VR-12 was derived from the Veterans RAND 36 Item Health Survey (VR-36) and contains
45 twelve items relating to quality of life, including physical and mental health, as well as specific questions
46 about functional status. Physical and Mental Health Summary Scores will be calculated. The VR-12 has
47 been validated and is widely applied as a metric for tracking health-related quality of life in the United
48 States.[31]
49
50

51 Functional status: We will assess functional status with the Barthel Index for Activities of Daily Living and
52 Lawton Instrumental Activities of Daily Living Scale. The Barthel Index is a measure of patient
53 performance in ten activities comprised of eight questions about personal care and two questions about
54 mobility. The Lawton Scale assesses independent living skills in 8 areas of function.
55
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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 $\alpha=0.05$, 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

1
2
3 variables will be included in the model: age, sex, American Society of Anesthesiologists physical score,
4 and Charlson co-morbidity index. The following known or suggested risk factors cognitive decline will
5 also be included in the model: baseline cognitive function, education level, type of surgery,
6 randomization group, preoperative depression, preoperative vascular disease, postoperative
7 complications, composite score on frailty tests and a history of falls. We will use a model with backward
8 elimination, to avoid exclusion of predictors with suppressor effects. While cognition will be entered as a
9 continuous variable, we will consider a change of one standard deviation in cognitive score as a minimal
10 clinically important difference.
11
12

13 Specific Aim 2: Evaluate whether patients who experience POD have worse quality of life at
14 approximately one year postoperatively.
15

16 The primary endpoint of our analysis is quality of life one year after surgery, as measured by the change
17 in VR-12 score between preoperative and postoperative assessments. Again, a multivariable regression
18 analysis will be performed to evaluate whether the development of postoperative delirium is an
19 independent predictor variable for the change in quality of life. POD will be entered as two categorical
20 variables: for incidence (present or absent) and for duration (<3 days POD or ≥3 days POD). The
21 following variables will be included in the model: age, sex, American Society of Anesthesiologists
22 physical score, Charlson co-morbidity index, type of surgery, randomization group, preoperative
23 depression, preoperative vascular disease, postoperative complications, cognitive function, composite
24 score on frailty tests and a history of falls. As above, we will use a model with backward elimination, to
25 avoid exclusion of predictors with suppressor effects. Previous work by our group has calculated the
26 minimal clinically important difference for overall VR-12 quality of life to be 1.4 for improvement and 3.6
27 for deterioration.[33]
28
29
30

31 For the above aims, we expect this study to be limited by loss to follow-up, estimated to be 50%. Those
32 lost to follow-up are likely to have more severe disease or deterioration in health. In order to determine
33 the influence of missing data in our analysis, we will also conduct a sensitivity analysis. We will calculate
34 the average cognition scores of those who declined. We will repeat the above models including missing
35 subjects, assuming all patients who did not participate had cognitive decline, quantified by the average
36 calculated from participants above. Additionally, to examine whether our sample selection method may
37 bias the results, we will compare baseline characteristics of those ENGAGES patients who were eligible
38 for our study to those who were not eligible.
39
40

41 Specific Aim 3: Explore whether patients who experience POD are more likely to become demented
42 within approximately one to two years of their surgery.
43

44 The primary endpoint of our analysis is incident dementia. A Cox proportional hazards regression will be
45 used to explore the likelihood of incident dementia associated with POD. POD will be entered as a
46 dichotomous variable (absent or present). The following variables will be included in the model: age,
47 sex, American Society of Anesthesiologists physical score, Charlson co-morbidity index, preoperative
48 cognitive function, type of surgery, randomization group, preoperative depression, preoperative
49 vascular disease, postoperative complications, and composite score on frailty tests and a history of falls.
50
51

52 All statistical analyses will be performed using SAS, version 9.4 (SAS Institute, Inc., Cary, North Carolina).
53 All other tests will be two-sided. By arbitrary convention all tests will be two-sided and considered
54 statistically significant at a $p < 0.05$, and all results will be presented with estimates and 95% confidence
55 intervals.
56

57 **Pre-specified additional analyses and sub-studies**

58
59
60

1
2
3 The primary aim of this study is to determine whether postoperative delirium predicts intermediate-
4 term cognitive impairment. However, as a sub-study of ENGAGES and SATISFY-SOS, several other
5 clinically relevant outcomes can be explored as well. SATISFY-SOS systematically collects detailed
6 information regarding patient centered outcomes, including patient perceived cognition. Correlation
7 between performance on neurocognitive testing and patient perceived cognition would be interesting
8 and useful clinically. Furthermore, the information regarding patients' characteristics will allow
9 exploration of risk factors for intermediate-term cognitive impairment. To investigate effects on
10 memory, we will perform a secondary analysis comparing the results of the SBT. Lastly, as part of
11 ENGAGES, some patients will have baseline NIH Toolbox cognitive testing, allowing description of long-
12 term cognitive trajectories as evaluated by these tests.
13
14

15 **Limitations**

16
17 This study contains several limitations. First, of most concern is the potential for non-response bias if
18 patients who do not participate are not a random subset of those contacted. We will attempt to
19 minimize the non-response rate by offering to visit patients at their homes if patients are unwilling to
20 come to the study center. We expect that those lost to follow-up would be more likely to have more
21 severe disease or health deterioration, potentially affecting cognitive function. We will thus conduct
22 appropriate sensitivity analyses to determine how missing outcomes data could alter the findings of our
23 study. Second, with an observational study, we cannot establish a causal relationship between
24 postoperative delirium and persistent declines in cognitive and quality of life. If an independent
25 relationship is found, we shall not be able to disambiguate whether postoperative delirium in some way
26 causes persistent decline in these outcomes, or whether it is a sign of underlying vulnerability. However,
27 since it is not possible to randomize patients to experience delirium, this limitation might be inevitable.
28 Third, since patients in this study are recruited from a single tertiary care center, the study sample may
29 not be representative of surgical patients in general. While these patients tend to have higher comorbid
30 disease burden than the general surgical population, including comorbidities in the statistical model will
31 account for these differences. Finally, while we have baseline cognitive assessments, we do not have
32 preoperative cognitive trajectories, and thus cannot determine whether the results of cognitive function
33 tests are a deviation from the pre-operative trend.
34
35
36
37
38
39

40 **Compliance**

41 **Subject Compliance**

42
43 The exposure of this study is post-operative delirium, so no monitoring of exposure compliance is
44 necessary. Methods to improve completion of one-year cognitive testing are described in Section 10.3,
45 "Limitations."
46
47

48 **Withdrawal of subjects**

49
50 Subjects may be withdrawn from the study only if requested by the patient. The reason for withdrawal
51 is recorded by the team's clinical project specialist.
52
53

54 **Ethical Considerations**

55
56
57
58
59
60

1
2
3 This study has been approved by the home institution's Institutional Review Board (IRB ID # 201407128).
4 Written, informed consent is obtained from all participants. As described in Section 7, "Study Groups,"
5 no special allowances are made for patients who are blind, deaf, illiterate or not fluent in English.
6 Participants may withdraw from the study at any time.
7
8
9

10 **Finance and Insurance**

11
12 Since this study involves only cognitive testing and surveys, it involves no more than minimal risk to the
13 patients. Finance details, insurance details, and cover for negligent and non-negligent harm are
14 therefore not relevant in this study.
15
16
17

18 **Reporting and Dissemination**

19
20 Results of this study will be published in a scientific journal. Participants will only be notified individually
21 if discoveries are made that directly impact their health.
22
23
24

25 **Author Contributions**

26
27 Authorship for this study will be given to key personnel involved in study design, recruitment, data
28 collection and data analysis. There are no publication restrictions, and no professional writers will be
29 involved in the generation of the manuscript. MSA, AA, JZC, MM, RT, TW, EL are responsible for
30 conceptualizing study design. AA, JZC, RT, MM, HM, and AM were responsible for recruitment,
31 enrollment, data collection and editing the protocol. AA, JZC, and RT are responsible for drafting the
32 protocol. All authors including AA, JZC, MM, RT, AM, HM, NL, TW, EL, and MSA have critically revised the
33 protocol and approved the final version.
34
35
36
37

38 **Acknowledgement**

39
40 We thank Ms. Michelle Doering, a medical librarian at Becker Medical Library at Washington University
41 School of Medicine for developing the systemic search criteria.
42
43
44
45

46 **Competing Interests**

47
48 The authors and contributors have no competing interests to disclose.
49
50
51

52 **Grant Information**

53
54 Funding for this study was awarded by the Foundation for Anesthesia Education and Research (award
55 reference ID RFG-08/15/2016-Aranake-Chrisinger). Funding for the ENGAGES trial was through a
56 UH2/UH3 mechanism grant awarded by the National Institute on Aging (1UH2AG050312-01). Funding
57
58
59
60

1
2
3 for the SATISFY-SOS study was from a grant awarded by the Barnes-Jewish Hospital Foundation (7937-
4 77) and support provided by the Department of Anesthesiology at Washington University.
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

References

1. Bedford, P.D., *Adverse cerebral effects of anaesthesia on old people*. Lancet, 1955. **269**(6884): p. 259-63.
2. Moller, J.T., et al., *Long-term postoperative cognitive dysfunction in the elderly ISPOCD1 study. ISPOCD investigators. International Study of Post-Operative Cognitive Dysfunction*. Lancet, 1998. **351**(9106): p. 857-61.
3. Monk, T.G., et al., *Predictors of cognitive dysfunction after major noncardiac surgery*. Anesthesiology, 2008. **108**(1): p. 18-30.
4. Selnes, O.A., et al., *Cognition 6 years after surgical or medical therapy for coronary artery disease*. Ann Neurol, 2008. **63**(5): p. 581-90.
5. Avidan, M.S., et al., *Long-term cognitive decline in older subjects was not attributable to noncardiac surgery or major illness*. Anesthesiology, 2009. **111**(5): p. 964-70.
6. Dokkedal, U., et al., *Cognitive Functioning after Surgery in Middle-aged and Elderly Danish Twins*. Anesthesiology, 2016. **124**(2): p. 312-21.
7. *Projected Future Growth of the Older Population*. [cited 2016 02/22]; Available from: http://www.aoa.gov/AoARoot/Aging_Statistics/future_growth/future_growth.aspx - age.
8. Whitlock, E.L., A. Vannucci, and M.S. Avidan, *Postoperative delirium*. Minerva Anestesiol, 2011. **77**(4): p. 448-56.
9. Gottesman, R.F., et al., *Delirium after coronary artery bypass graft surgery and late mortality*. Ann Neurol, 2010. **67**(3): p. 338-44.
10. Koster, S., et al., *Consequences of delirium after cardiac operations*. Ann Thorac Surg, 2012. **93**(3): p. 705-11.
11. Bickel, H., et al., *High risk of cognitive and functional decline after postoperative delirium. A three-year prospective study*. Dement Geriatr Cogn Disord, 2008. **26**(1): p. 26-31.
12. Saczynski, J.S., et al., *Cognitive trajectories after postoperative delirium*. N Engl J Med, 2012. **367**(1): p. 30-9.
13. Jankowski, C.J., et al., *Cognitive and functional predictors and sequelae of postoperative delirium in elderly patients undergoing elective joint arthroplasty*. Anesth Analg, 2011. **112**(5): p. 1186-93.
14. Ballard, C., et al., *Optimised anaesthesia to reduce post operative cognitive decline (POCD) in older patients undergoing elective surgery, a randomised controlled trial*. PLoS One, 2012. **7**(6): p. e37410.
15. Abildstrom, H., et al., *Cognitive dysfunction 1-2 years after non-cardiac surgery in the elderly. ISPOCD group. International Study of Post-Operative Cognitive Dysfunction*. Acta Anaesthesiol Scand, 2000. **44**(10): p. 1246-51.
16. Cormack, F., et al., *A meta-analysis of cognitive outcome following coronary artery bypass graft surgery*. Neurosci Biobehav Rev, 2012. **36**(9): p. 2118-29.
17. Kat, M.G., et al., *Long-term cognitive outcome of delirium in elderly hip surgery patients. A prospective matched controlled study over two and a half years*. Dement Geriatr Cogn Disord, 2008. **26**(1): p. 1-8.
18. Inouye, S.K., et al., *The short-term and long-term relationship between delirium and cognitive trajectory in older surgical patients*. Alzheimers Dement, 2016. **12**(7): p. 766-75.
19. Gunther, M.L., et al., *The association between brain volumes, delirium duration, and cognitive outcomes in intensive care unit survivors: the VISIONS cohort magnetic resonance imaging study**. Crit Care Med, 2012. **40**(7): p. 2022-32.
20. Morandi, A., et al., *The relationship between delirium duration, white matter integrity, and cognitive impairment in intensive care unit survivors as determined by diffusion tensor imaging:*

- 1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
- the VISIONS prospective cohort magnetic resonance imaging study**. Crit Care Med, 2012. **40**(7): p. 2182-9.
21. Wacker, P., et al., *Post-operative delirium is associated with poor cognitive outcome and dementia*. Dement Geriatr Cogn Disord, 2006. **21**(4): p. 221-7.
 22. Lingehall, H.C., et al., *Preoperative Cognitive Performance and Postoperative Delirium Are Independently Associated With Future Dementia in Older People Who Have Undergone Cardiac Surgery: A Longitudinal Cohort Study*. Crit Care Med, 2017.
 23. Schenning, K.J., et al., *Surgery is associated with ventricular enlargement as well as cognitive and functional decline*. Alzheimers Dement, 2015.
 24. Abelha, F.J., et al., *Outcome and quality of life in patients with postoperative delirium during an ICU stay following major surgery*. Crit Care, 2013. **17**(5): p. R257.
 25. Kastaun, S., et al., *The Relevance of Postoperative Cognitive Decline in Daily Living: Results of a 1-Year Follow-up*. J Cardiothorac Vasc Anesth, 2016. **30**(2): p. 297-303.
 26. Wildes, T.S., et al., *Protocol for the Electroencephalography Guidance of Anesthesia to Alleviate Geriatric Syndromes (ENGAGES) study: a pragmatic, randomised clinical trial*. BMJ Open, 2016. **6**(6): p. e011505.
 27. Helsten, D.L., et al., *Methodologic Considerations for Collecting Patient-reported Outcomes from Unselected Surgical Patients*. Anesthesiology, 2016. **125**(3): p. 495-504.
 28. Bleck, T.P., et al., *What is the NIH toolbox, and what will it mean to neurology?* Neurology, 2013. **80**(10): p. 874-5.
 29. Weintraub, S., et al., *Cognition assessment using the NIH Toolbox*. Neurology, 2013. **80**(11 Suppl 3): p. S54-64.
 30. Carpenter, C.R., et al., *Four sensitive screening tools to detect cognitive dysfunction in geriatric emergency department patients: brief Alzheimer's Screen, Short Blessed Test, Ottawa 3DY, and the caregiver-completed AD8*. Acad Emerg Med, 2011. **18**(4): p. 374-84.
 31. Selim, A.J., et al., *Updated U.S. population standard for the Veterans RAND 12-item Health Survey (VR-12)*. Qual Life Res, 2009. **18**(1): p. 43-52.
 32. Xie, J., et al., *Survival times in people with dementia: analysis from population based cohort study with 14 year follow-up*. BMJ, 2008. **336**(7638): p. 258-62.
 33. Kronzer, V.L., et al., *Changes in quality of life after elective surgery: an observational study comparing two measures*. Qual Life Res, 2017. **26**(8): p. 2093-2102.

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

For peer review only

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-COV5	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.
Rothenhauser 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

1. Tow, A., et al., *Cognitive Reserve and Postoperative Delirium in Older Adults*. J Am Geriatr Soc, 2016. **64**(6): p. 1341-6.
2. Neufeld, K.J., et al., *Long-Term Outcomes of Older Adults with and Without Delirium Immediately After Recovery from General Anesthesia for Surgery*. Am J Geriatr Psychiatry, 2015. **23**(10): p. 1067-74.
3. Sprung, J., et al., *Association of mild cognitive impairment with exposure to general anesthesia for surgical and nonsurgical procedures: a population-based study*. Mayo Clin Proc, 91 (2) (2016), pp. 208-217.
4. Hempenius, L., et al., *Long Term Outcomes of a Geriatric Liaison Intervention in Frail Elderly Cancer Patients*. PLoS One, 2016. **11**(2): p. e0143364.
5. Youngblom, E., et al., *The temporal relationship between early postoperative delirium and postoperative cognitive dysfunction in older patients: a prospective cohort study*. Can J Anaesth, 2014. **61**(12): p. 1084-92.
6. Hussain, M., et al., *General anesthetic and the risk of dementia in elderly patients: current insights*. Clin Interv Aging, 2014. **9**: p. 1619-28.
7. Abelha, F.J., et al., *Outcome and quality of life in patients with postoperative delirium during an ICU stay following major surgery*. Crit Care, 2013. **17**(5): p. R257.
8. Witlox, J., et al., *The neuropsychological sequelae of delirium in elderly patients with hip fracture three months after hospital discharge*. Int Psychogeriatr, 2013. **25**(9): p. 1521-31.
9. Radtke, F.M., et al., *Monitoring depth of anaesthesia in a randomized trial decreases the rate of postoperative delirium but not postoperative cognitive dysfunction*. Br J Anaesth, 2013. **110** Suppl 1: p. i98-105.

10. Saczynski, J.S., et al., *Cognitive trajectories after postoperative delirium*. N Engl J Med, 2012. **367**(1): p. 30-9.
11. Koster, S., et al., *Consequences of delirium after cardiac operations*. Ann Thorac Surg, 2012. **93**(3): p. 705-11.
12. Quinlan, N. and J.L. Rudolph, *Postoperative delirium and functional decline after noncardiac surgery*. J Am Geriatr Soc, 2011. **59 Suppl 2**: p. S301-4.
13. Wallbridge, H.R., et al., *Risk factors for postoperative cognitive and functional difficulties in abdominal aortic aneurysm patients: a three month follow-up*. Int J Geriatr Psychiatry, 2011. **26**(8): p. 818-24.
14. Jankowski, C.J., et al., *Cognitive and functional predictors and sequelae of postoperative delirium in elderly patients undergoing elective joint arthroplasty*. Anesth Analg, 2011. **112**(5): p. 1186-93.
15. Rudolph, J.L., et al., *Delirium: an independent predictor of functional decline after cardiac surgery*. J Am Geriatr Soc, 2010. **58**(4): p. 643-9.
16. Koster, S., A.G. Hensens, and J. van der Palen, *The long-term cognitive and functional outcomes of postoperative delirium after cardiac surgery*. Ann Thorac Surg, 2009. **87**(5): p. 1469-74.
17. Gogol, M., [Delirium in the elderly]. Z Gerontol Geriatr, 2008. **41**(6): p. 431-9.
18. Bickel, H., et al., *High risk of cognitive and functional decline after postoperative delirium. A three-year prospective study*. Dement Geriatr Cogn Disord, 2008. **26**(1): p. 26-31.
19. Kat, M.G., et al., *Long-term cognitive outcome of delirium in elderly hip surgery patients. A prospective matched controlled study over two and a half years*. Dement Geriatr Cogn Disord, 2008. **26**(1): p. 1-8.
20. Rudolph, J.L., et al., *Delirium is associated with early postoperative cognitive dysfunction*. Anaesthesia, 2008. **63**(9): p. 941-7.
21. Olofsson, B., et al., *Delirium is associated with poor rehabilitation outcome in elderly patients treated for femoral neck fractures*. Scand J Caring Sci, 2005. **19**(2): p. 119-27.
22. Rothenhausler, H.B., et al., *Psychiatric and psychosocial outcome of cardiac surgery with cardiopulmonary bypass: a prospective 12-month follow-up study*. Gen Hosp Psychiatry, 2005. **27**(1): p. 18-28.
23. Duppils, G.S. and K. Wikblad, *Cognitive function and health-related quality of life after delirium in connection with hip surgery. A six-month follow-up*. Orthop Nurs, 2004. **23**(3): p. 195-203.
24. Edelstein, D.M., et al., *Effect of postoperative delirium on outcome after hip fracture*. Clin Orthop Relat Res, 2004(422): p. 195-200.
25. Adunsky, A., et al., *The unfavorable nature of preoperative delirium in elderly hip fractured patients*. Arch Gerontol Geriatr, 2003. **36**(1): p. 67-74.
26. Lundstrom, M., et al., *Dementia after delirium in patients with femoral neck fractures*. J Am Geriatr Soc, 2003. **51**(7): p. 1002-6.
27. Edlund, A., et al., *Clinical profile of delirium in patients treated for femoral neck fractures*. Dement Geriatr Cogn Disord, 1999. **10**(5): p. 325-9.
28. Goldstein, M.Z., B.S. Fogel, and B.L. Young, *Effect of elective surgery under general anesthesia on mental status variables in elderly women and men: 10-month follow-up*. Int Psychogeriatr, 1996. **8**(1): p. 135-49.

Appendix B.

Patient Recruitment

~10,000 patients/year enrolled in SATISFY-SOS study
(offered to all surgical patients at the BJC preoperative clinic >18
years old requiring anesthesia services)

Patients enrolled in the ENGAGES study
(must be >60 years old undergoing major elective
surgery with general anesthesia and
anticipated hospital stay >2 days)

Baseline assessment completed

1,232 patients randomized in the
ENGAGES study to receive EEG-
guided anesthesia or standard-of-
care anesthesia

Patients are assessed for delirium
daily up to POD 5

200 patients enrolled in this
observational study 10 -16 months
after surgery, where researchers are
blinded to randomization and
postoperative delirium status

Patients excluded from the
observational study if:

- Patient did not have surgery
- Patient with no follow-up
appointment in the 10-16 month
time period and lives >45 miles away
- Patient declined participation
- Patient deceased before one year

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) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —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 <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	6-7
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —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) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	8-9

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

(e) Describe any sensitivity analyses

Continued on next page

For peer review only

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 (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	N/A
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time <i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure <i>Cross-sectional study</i> —Report numbers of outcome events or summary measures	N/A
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 (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	N/A
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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2017-017079.R2
Article Type:	Protocol
Date Submitted by the Author:	17-Oct-2017
Complete List of Authors:	Aranake-Chrisinger, Amrita; Washington University in Saint Louis School of Medicine, Anesthesiology Cheng, Jenny; Washington University in Saint Louis School of Medicine, Anesthesiology Muench, Maxwell; Washington University in Saint Louis School of Medicine, Anesthesiology; Kirksville College of Osteopathic Medicine, Tang, Rose; Washington University in Saint Louis School of Medicine, Anesthesiology Mickle, Angela; Washington University in Saint Louis School of Medicine, Anesthesiology Maybrier, Hannah; Washington University in Saint Louis School of Medicine, Anesthesiology Lin, Nan; Washington University in Saint Louis, Mathematics; Division of Biostatistics Wildes, Troy; Washington University in Saint Louis School of Medicine, Anesthesiology Lenze, Eric Avidan, Michael; Washington University School of Medicine, Anesthesiology
Primary Subject Heading:	Anaesthesia
Secondary Subject Heading:	Geriatric medicine, Neurology
Keywords:	postoperative delirium, postoperative cognitive decline, EEG guidance, quality of life, Dementia < NEUROLOGY, frailty

SCHOLARONE™
Manuscripts

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

Protocol Authors:

Amrita Aranake, MD, primary project investigator, aranakea@wustl.edu

Jenny Zhao Cheng, BS, j.cheng@wustl.edu

Maxwell Muench, BS, mrmuench@atsu.edu

Rose Tang, BS, tang.r@wustl.edu

Angela Mickle, MS, micklean@wustl.edu

Hannah Maybrier, BS, h.maybrier@wustl.edu

Nan Lin, MS, PhD, nlin@wustl.edu

Troy Wildes, MD, wildest@wustl.edu

Eric Lenze, MD, lenzee@wustl.edu

Michael S Avidan, MBBCh¹, avidanm@wustl.edu

Corresponding Author:

Michael Avidan, avidanm@wustl.edu

660 S Euclid Ave, Campus Box 8054

Saint Louis, MO 63110

P: 314-747-4155 F: 314-747-3977

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 $\alpha=0.05$.

1
2
3 **Ethics and Dissemination:** The study has been approved by the Washington University in St. Louis
4 Institutional Review Board (IRB #201601099). Plans for dissemination include scientific publications and
5 presentations at scientific conferences.
6

7 **Trial registration:** This is a pre-specified sub-study of ENGAGES (NCT02241655).
8

9 **Strengths and Limitations of this study:**

10 *Strengths:*

- 11 • Postoperative intermediate term cognitive function and quality of life are important patient-
- 12 centered outcomes.
- 13 • Analysis will include salient patient characteristics, including preoperative cognition, comorbid
- 14 conditions and frailty.
- 15 • Study sample will consist of an understudied population in clinical research.
- 16
- 17
- 18
- 19
- 20

21 *Limitations:*

- 22 • Potential for loss to follow-up and non-response bias
- 23 • Since this is an observational study, we cannot establish a causal relationship between
- 24 postoperative delirium and persistent declines in cognition and quality of life.
- 25 • We cannot determine whether cognitive function deviates from the pre-operative trend,
- 26 without multiple preoperative cognitive assessments to establish a trajectory.
- 27
- 28
- 29
- 30

31 **Background**

32
33 Since Bedford's 1955 case series suggesting an association between surgical intervention and cognitive
34 impairment, there has been growing concern among the public that cognitive decline is a common
35 consequence of surgery.[1] This pervasive view continues to concern patients and their families, fueled
36 by anecdotal evidence and media coverage. Postoperative cognitive decline (POCD) has been a growing
37 topic for scientific investigation after several studies were published by the International Study of Post-
38 Operative Cognitive Dysfunction (ISPOCD) group. While several influential studies demonstrated early
39 postoperative cognitive decline (POCD) lasting up to 3 months, the persistence of this cognitive decline
40 has been controversial.[2-6] Importantly, the population of Americans older than 60 years is projected
41 to double over the next 30 years,[7] and many will require surgery. Acute and long-term cognitive
42 changes related to surgical intervention are particularly distressing to patients and their families.
43 Therefore, clarification of cognitive outcomes would assist patients and practitioners in making an
44 informed decision about the relative risks and benefits of proceeding with elective surgery.
45
46
47

48 **Literature search and review**

49
50 A systemized literature review was conducted with the help of a librarian experienced in systemic
51 review (see Acknowledgement). Ovid Medline was searched for studies published between 1981 and
52 September 2016 using the query: Postoperative or after surgery AND Delirium AND Cognitive function
53 or dementia AND Elderly AND Long-term or intermediate term or follow up or cohort studies or
54 retrospective studies. Articles in English or with English translation were considered. JC and RT reviewed
55 the 301 search results and found 28 articles that were relevant to our clinical question. 21 out of the 28
56 relevant articles (75%) showed significant result in the relationship between postoperative delirium
57
58
59
60

1
2
3 (POD) and intermediate- to long-term cognitive decline (Appendix A). These seem to suggest a high pre-
4 test probability in studying the ability of POD to predict intermediate-term cognitive decline. However,
5 these studies are heterogeneous in the study design, selected surgical patient population, and outcome
6 measurement tools complicating synthesis of the systemic search to draw conclusions.
7

8
9 POD is a common complication for surgical patients over the age of 60 years.[8] It is a neurological
10 syndrome characterized by acute and fluctuating disturbances in awareness and attention that
11 represent a change from baseline; in addition to these cardinal features, the diagnosis of delirium
12 requires at least one additional cognitive symptom and the absence of medical conditions that might
13 explain these disturbances. Although usually transient, POD has been associated with several salient
14 adverse outcomes, including mortality, prolonged ICU stay and persistent cognitive decline.[9-12] One
15 prospective cohort study of cardiac surgery patients suggested patients experiencing POD had
16 prolonged cognitive impairment at one year, and those with longer duration of delirium had slower
17 recovery.[12] However, after adjusting for baseline differences in cognitive function, there was no
18 significant difference compared with controls. The same study also demonstrated that mild cognitive
19 impairment preoperatively may predispose patients to delirium; thus POD may be exposing patients
20 who are already experiencing sub-clinical cognitive decline or those who have an underlying
21 vulnerability to cognitive decline. Another study, in orthopedic surgery patients found no association
22 between POD and cognitive decline at three months.[13] While several studies have suggested that
23 postoperative cognitive decline can persist past six months after surgery,[2, 14] others have
24 demonstrated a transient early decline with later recovery.[4, 5] Furthermore, there is conflicting
25 evidence regarding the long-term cognitive trajectories of postoperative patients, with some suggesting
26 overall improvement and others suggesting overall decline.[15, 16] POD has been posited as a risk factor
27 for lasting decline; however, few articles have addressed the association between POD and persistent
28 postoperative cognitive decline (arbitrarily defined as lasting >6 months). A prospective matched
29 controlled survey with an average of 30-month follow-up demonstrated that dementia or mild cognitive
30 impairment was diagnosed in 77.8% of the surviving hip surgery patients with POD, almost doubling the
31 40.9% rate of control patients (relative risk = 1.9, 95% CI = 1.1-3.3). However the study was
32 underpowered to evaluate the long-term cognitive function, as the power calculation was based on the
33 original study and no intermediate assessments were made to track patients' cognitive function.[17]
34 Another prospective cohort study followed patients over 36 months and found that patients with POD
35 initially had cognitive decline with a transient recovery, but then exhibited an accelerated pace of long-
36 term cognitive decline when compared to controls.[18] Overall, the results of these studies suggest an
37 association between POD and persistent cognitive impairment, however compelling data supporting an
38 independent association are lacking. Many of these studies also do not consider the duration of
39 delirium, which may portend long-term cognitive decline.[19, 20]
40
41
42
43
44

45 Pre-existing dementia or cognitive impairment is a known risk factor for POD,[8] and several studies
46 suggest an association between POD and dementia. One study in elderly orthopedic surgery patients
47 reported a relative risk of dementia in patient with POD of 10.5 compared to those without POD.[21] A
48 recent study demonstrated a similar association in elderly cardiac surgery patients.[22] However it
49 remains unclear whether POD causes, accelerates, or signifies an underlying vulnerability to cognitive
50 impairment, thus further investigation is warranted.
51
52

53 In addition to cognitive outcomes, quality of life and functional capacity are also important patient-
54 centered outcomes that require further investigation. While one study found that elderly surgical
55 patients tended to have long-term cognitive and functional decline compared to non-surgical
56 patients,[23] few studies have examined the association between cognitive function and quality of life
57 or activities of daily living. One prospective study over a 10-month period demonstrated that delirium
58
59
60

1
2
3 was an independent risk factor for becoming dependent for personal activities of daily living after ICU
4 discharge (OR = 2.188, P <0.046) and that patients with POD also demonstrated a greater decline in
5 Short-Form-36 domains after discharge, especially in physical function, vitality, and social function.[24]
6 However, this study could not draw conclusions regarding cognitive function due to lack of data.
7 Kastaun et al. reported perceived impairment in ability to perform activities of daily living one year after
8 surgery, however did not detect significant cognitive decline at that time.[25] It remains unclear
9 whether cognitive decline results in impaired functional capacity or decreased quality of life. In fact,
10 given the variable definitions of POCD, data from previous studies are difficult to interpret. As many of
11 the deficits found in neuropsychiatric testing are subtle, it is possible that detected cognitive impairment
12 has no clinically significant impact on these patient-centered outcomes. Instead of using an arbitrary
13 threshold to dichotomize cognitive function as normal or impaired, it would be more informative to
14 correlate these outcomes with cognitive function as a continuous variable or stratified into multiple
15 groups.
16
17
18

19 At our institution, patient reported postoperative outcomes are gathered as part of the Systematic
20 Assessment and Targeted Improvement of Services Following Yearlong Surgical Outcomes Surveys
21 (SATISFY-SOS) initiative (NCT02032030). Additionally, the ongoing randomized controlled trial:
22 Electroencephalography (EEG) Guidance of Anesthesia to Alleviate Geriatric syndromes (ENGAGES)
23 study, is evaluating patients for postoperative delirium.[26] Using the scaffold provided by these studies,
24 we aim to identify whether delirium is an independent predictor for intermediate-term cognitive
25 function and quality of life.
26
27

28 **Justification**

29
30 The population of older adults is projected to double over the next thirty years, and many will undergo
31 elective surgery with the hope of overall improvement in health and quality of life. Postoperative
32 delirium is a common and potentially preventable complication, thus clarification of its association with
33 persistent declines in cognition and quality of life will inform perioperative care. Prior studies have not
34 demonstrated an association independent of pre-existing patient characteristics and perioperative
35 course. The proposed study addresses the methodologic concerns in current literature by: 1. objectively
36 evaluating attention and executive function with validated cognitive tests, 2. obtaining measurements of
37 baseline cognitive function, 3. conducting statistical analysis which includes important potential
38 confounding factors including frailty measures, and 4. sampling from an unselected surgical population.
39 Given that delirium is predominantly a disorder of attention and executive function, we will focus our
40 investigation on these cognitive domains. The results of this study will contribute to the broader
41 understanding of postoperative cognitive changes, and may help identify and provide therapies for
42 susceptible patients earlier to ultimately improve outcomes.
43
44
45

46 As part of the ENGAGES study, patients have been enrolling since January 2015, with 804 patients
47 enrolled thus far. Over the last year, the ENGAGES research team has enrolled approximately 35
48 patients per month, and has gathered baseline cognitive data on a majority of participants. Preliminary
49 screening suggests about 65% of those enrolled in ENGAGES are eligible for the current study.
50 Anticipating that half of those contacted will enroll, we expect to assess 10 to 15 patients per month.
51 The scaffold of ENGAGES and trained study members make this sub-study highly feasible.
52
53
54

55 **Specific Aims**

56
57
58
59
60

1
2
3 **Specific Aim #1:** Determine whether the incidence and duration of postoperative delirium predict worse
4 performance on specific cognitive tests at approximately one year after surgery.
5

6 We hypothesize that postoperative delirium is independently associated with poorer performance on
7 tests of attention and executive function at one year after surgery, and that patients with a longer
8 duration of delirium will have more marked cognitive decrement. We will conduct a regression analysis,
9 including likely contributory variables, to assess the association between delirium and cognitive decline
10 at approximately one year.
11

12
13 **Specific Aim #2:** Evaluate whether the incidence and duration of postoperative delirium predict worse
14 quality of life at approximately one year postoperatively.
15

16 We hypothesize that postoperative delirium is independently associated with decreased quality of life
17 one year after surgery, and that patients with a longer duration of delirium will have more marked
18 decrease in health-related quality of life. We will conduct a regression analysis, including likely
19 contributory variables, to assess the association between delirium and health-related quality of life at
20 approximately one year.
21

22
23 **Specific Aim #3:** Explore whether patients who experience postoperative delirium are more likely to
24 develop dementia within approximately one to two years of their surgery.
25

26 We hypothesize that postoperative delirium is independently associated with incident dementia one to
27 two years after surgery. We will conduct a Cox proportional hazards regression, including likely
28 contributory variables, to assess the rate of incident dementia approximately one to two years after
29 surgery.
30

31 32 33 **Study Design:**

34
35 This prospective cohort study is pre-specified sub-study of the ENGAGES study. The ENGAGES study is a
36 randomized clinical trial enrolling approximately 1,200 patients sixty years and older who will undergo
37 elective major surgery at Barnes Jewish Hospital (BJH), St. Louis, MO.
38

39 The parent trial will recruit patients primarily from the Center for Preoperative Assessment and Planning
40 (CPAP) clinic. Among inclusion criteria for ENGAGES, details of which have been previously
41 published,[26] is enrollment in the SATISFY-SOS study.[27] As part of ENGAGES, participants will
42 complete a comprehensive baseline assessment including cognitive tests, frailty measures, and
43 screening for delirium and dementia. Postoperatively, patients will have daily evaluations for delirium
44 during the hospital stay. The current study will retrospectively identify 200 participants who reside
45 within approximately 45 miles from the hospital or those who have a planned visit to the hospital
46 between ten to sixteen months post-operatively. Patients diagnosed with delirium postoperatively will
47 be compared to those without delirium. A prospective intermediate-term postoperative assessment will
48 be conducted by a research team member blinded to whether the patient developed postoperative
49 delirium.
50
51
52

53 54 55 **Study Groups**

56
57
58
59
60

1
2
3 The target population for this study is patients who underwent preoperative assessment for elective
4 surgery at the Center for Preoperative Assessment and Planning (CPAP) clinic at Barnes Jewish Hospital
5 (BJC) in St. Louis, Missouri. The ENGAGES study is enrolling 1,232 patients who are already enrolled in
6 the SATISFY-SOS study. Inclusion criteria include patients sixty years old and older, who are competent
7 to provide informed consent and who are undergoing major elective surgery under general anesthesia
8 with a potent volatile anesthetic agent that requires a minimum stay of two days postoperatively (i.e.,
9 open cardiac surgery, open thoracic surgery, major vascular surgery, intra-abdominal surgery, open
10 gynecologic surgery, open urologic surgery, major orthopedic surgery, open hepato-biliary surgery and
11 major ear, nose and throat surgery). The ENGAGES study has minimal exclusion, as there are no absolute
12 contraindications to EEG monitoring. Exclusion criteria include neurosurgical procedures, preoperative
13 delirium, patients who are unable to participate adequately in delirium screening, including those who
14 are blind, deaf, illiterate, or not fluent in English, patients with a history of intraoperative awareness
15 during intended general anesthesia, and patients who had a second surgery planned within five days
16 after the index surgery. This prospective study will enroll 200 patients who are already enrolled in the
17 ENGAGES and SATISFY-SOS studies (Appendix B). In addition to previously described inclusion and
18 exclusion criteria, participants will be included in this study if their home residence is ≤ 45 miles from BJH
19 or they have a planned visit to the hospital within the specified timeframe. Patients who have not
20 completed the baseline cognitive assessment with Trails A, Trails B and the Stroop Color Word Test will
21 also be excluded from this study.
22
23
24
25
26
27

28 **Recruitment**

29
30 As part of the SATISFY-SOS study, patients have given informed consent to be contacted by Washington
31 University for follow-up of health-related outcomes up to a year after surgery. Eligible participants will
32 be identified by chart review and query of the ENGAGES REDCap database. A member of the research
33 team will contact potential participants by telephone approximately ten to sixteen months after surgery
34 for enrollment in this study. Patients may refuse participation in the study. If patients agree to
35 participation, written consent will be obtained when the patient comes in for assessment, prior to any
36 data collection. Patients will then be prospectively evaluated with assessments of cognition, quality of
37 life, and frailty measures, which are described in detail below. Meal vouchers will be provided for
38 participation. Patients residing within approximately 45 miles of the hospital, who are willing to
39 participate in the study, but unable or unwilling to come to the study center will be offered assessment
40 at home by a member of the research team. Additionally, ENGAGES patients who have not completed a
41 one-year dementia screening will be contacted by telephone approximately 18 to 24 months after
42 surgery. Phone consent will be obtained to complete dementia screening over the telephone.
43
44 Participants may refuse to participate.
45
46
47
48

49 **Data**

50 **Data Collection**

51
52 Routinely obtained baseline assessment in the CPAP clinic includes demographic information, a detailed
53 medical history, surgical history, medications and physical examination. As part of SATISFY-SOS and
54 ENGAGES, baseline assessment using the Barthel Index, Veteran's RAND 12-item Health Survey (VR-12),
55 Eight-item Interview to Differentiate Aging and Dementia (AD-8), Short Blessed Test (SBT), alcohol sniff
56 test, and Personal Health Questionnaire Depression Scale (PHQ8) will be performed. Baseline cognitive
57
58
59
60

1
2
3 function will be evaluated by the ENGAGES team with the Trails A and B, and the Stroop Color and Word
4 Test. Some patients may complete computer-based cognitive testing with the NIH toolbox at baseline
5 (described below). Additionally, frailty will be assessed using grip strength, Timed-up and Go (TUG) test,
6 and obtaining fall history at baseline. Participants will have daily delirium assessments by trained
7 researchers with the Confusion Assessment Method in the postoperative period for the duration of their
8 hospital stay. Data collected by the ENGAGES team will be entered into the Washington University
9 School of Medicine Research Electronic Data Capture (REDCap) application. [18] Perioperative data will
10 be retrieved from the hospital's perioperative electronic medical record (Metavision by iMDsoft®,
11 Needham, MA). High fidelity perioperative data is routinely captured from our EMR to an SQL server
12 (Microsoft, Redmond, WA) database. These data include bispectral index (BIS) values, EEG burst
13 suppression durations, laboratory data, intraoperative medications, physiological readings, and
14 postoperative recovery parameters. All the data for SATISFY-SOS are integrated from various data
15 sources and are stored in a single data repository housed in the Department of Anesthesiology at
16 Washington University.
17
18
19

20
21 Cognition: The primary outcome in this study will be a composite score comprised of scores from three
22 cognitive tests evaluating attention and executive function: Trails A, Trails B and Stroop Color Word Test.
23 These cognitive tests will be repeated approximately one year after surgery to evaluate intermediate
24 term cognitive function. The research team member performing the assessments will be blinded to
25 whether the patient developed postoperative delirium. In addition to the above tests, this study
26 proposes to use the Cognition Battery of the National Institutes of Health (NIH) Toolbox Assessment of
27 Neurological and Behavioral Function (<http://www.nihtoolbox.org>). The NIH Toolbox Cognition Battery
28 (Feinberg School of Medicine, Northwestern University, Chicago, IL), is a comprehensive yet concise
29 standardized computer-based assessment battery; we plan to include tasks to evaluate attention
30 (Flanker Inhibitory Control and Attention Test), episodic memory (Picture Sequence Memory Test), and
31 executive function (Dimensional Change Card Sort Test and Flanker Inhibitory Control and Attention
32 Test). Patients will complete the NIH Toolbox Cognition tests above, which takes approximately 10
33 minutes to complete. The NIH Toolbox Cognition Battery has been validated for use across a wide range
34 of ages.[28, 29] Self-reported cognitive function will be evaluated by The Patient Reported Outcomes
35 Measurement Information System (PROMIS). PROMIS, funded by the National Institutes of Health (NIH),
36 is a set of highly reliable, valid, flexible, precise, and responsive assessment tools that measure patient-
37 reported health status. PROMIS v1.0-Applied Cognition-General Concerns-Short Form 4a is comprised of
38 four questions about thinking and cognition. PROMIS v1.0-Applied Cognition-Abilities-Short Form 4a is
39 comprised of four questions about memory. Evaluation for dementia with the SBT will be completed for
40 all patients at baseline, and again between one to two years after surgery. The SBT has been shown to
41 have 95% sensitivity for detecting cognitive dysfunction when compared with the MMSE, and can be
42 administered in approximately 3 minutes, making it an excellent screening tool.[30]
43
44
45

46
47 Quality of Life: As part of the ongoing SATISFY-SOS study, patient self-reported Health-related Quality of
48 Life information will be assessed through the VR-12 at baseline (preoperatively) and also one year after
49 surgery. The VR-12 was derived from the Veterans RAND 36 Item Health Survey (VR-36) and contains
50 twelve items relating to quality of life, including physical and mental health, as well as specific questions
51 about functional status. Physical and Mental Health Summary Scores will be calculated. The VR-12 has
52 been validated and is widely applied as a metric for tracking health-related quality of life in the United
53 States.[31]
54

55
56 Functional status: We will assess functional status with the Barthel Index for Activities of Daily Living and
57 Lawton Instrumental Activities of Daily Living Scale. The Barthel Index is a measure of patient
58
59
60

1
2
3 performance in ten activities comprised of eight questions about personal care and two questions about
4 mobility. The Lawton Scale assesses independent living skills in 8 areas of function.
5

6
7 Frailty: Information regarding weight loss, endurance, and physical activity level are routinely collected
8 in the preoperative clinic and as part of SATISFY-SOS. We will also measure grip strength and the Timed
9 Up and Go (TUG) test. Grip strength will also be assessed with three measurements in the dominant
10 hand using a Jamar® handheld dynamometer (Lafayette Instruments, Lafayette, IN). Maximal grip
11 strength will be selected for analysis.
12

13 Table 1. contains details regarding variables to be collected for the study.
14

15 **Data management**

16
17 A customized database has been developed to facilitate data management for this study using the
18 Research Electronic Data Capture (REDCap) system. REDCap is a secure web-based data capture system
19 available to research groups receiving support from the Institute of Clinical and Translational Sciences at
20 Washington University. It is maintained by the Washington University Division of Biostatistics with
21 multiple capabilities to simplify data management and analysis. These include intuitive data entry, data
22 audit and tracking, import of externally sourced data, and automated data export for analysis. REDCap
23 requires unique user identification and password combinations for secure access.
24
25
26
27

28 **Statistical Consideration**

29 **Sample calculations**

30
31
32 For specific aims 1&2, sample size calculations have been performed using G*POWER 3.0.10. Power
33 analysis for a multiple regression with 15 predictors was conducted to determine a sufficient sample size
34 using an alpha of 0.05, a power of 0.9, and a medium effect size ($f^2 = 0.1$). Based on the aforementioned
35 assumptions, the desired sample size is 130 patients. We will plan to recruit 200 patients, which will
36 increase the power for the primary outcome and prevent overfitting of the regression model.
37
38

39 For specific aim 3, sample size calculation has been performed using PS 3.1.2. Based on results of a
40 previously published meta-analysis of four studies investigating the use of BIS-guided anesthetic
41 administration, we conservatively assume an incidence of POD of 25%. A previous study has reported
42 the median age at the onset of dementia to be approximately 84 years old.[32] To detect a hazard ratio
43 of 2.0 in patients with delirium compared to those without delirium, with 80% power and $\alpha=0.05$, we
44 will need 516 patients (129 in the delirium group, and 387 in the control group). To account for a 10%
45 attrition rate, we will recruit 570 patients.
46
47

48 **Statistical analysis**

49
50 We will perform and report descriptive statistics (mean and standard deviation) for all variables
51 between patients with and without the diagnosis of POD. Descriptive statistics will include chi-squared
52 tests for categorical variables, t-tests for normally distributed continuous variables and Mann-Whitney
53 tests for nonparametric continuous variables.
54

55 Specific Aim 1: Determine whether patients who experience POD perform worse on specific cognitive
56 tests at approximately one year after surgery.
57
58
59
60

1
2
3 The primary endpoint of our analysis is cognitive function one year after surgery, as measured by the
4 Trails A & B and the Stroop Color Word Test. Z-scores will be calculated for performance for each test,
5 and combined to form a composite measure. Multivariable regression analysis will be used to determine
6 whether the development of postoperative delirium is a predictor variable for cognitive function,
7 independent from other possible contributory factors. POD will be entered as two categorical variables:
8 for incidence (present or absent) and for duration (<3 days POD or ≥3 days POD). The following
9 variables will be included in the model: age, sex, American Society of Anesthesiologists physical score,
10 and Charlson co-morbidity index. The following known or suggested risk factors cognitive decline will
11 also be included in the model: baseline cognitive function, education level, type of surgery,
12 randomization group, preoperative depression, preoperative vascular disease, postoperative
13 complications, composite score on frailty tests and a history of falls. We will use a model with backward
14 elimination, to avoid exclusion of predictors with suppressor effects. While cognition will be entered as a
15 continuous variable, we will consider a change of one standard deviation in cognitive score as a minimal
16 clinically important difference.
17
18
19

20 Specific Aim 2: Evaluate whether patients who experience POD have worse quality of life at
21 approximately one year postoperatively.
22

23 The primary endpoint of our analysis is quality of life one year after surgery, as measured by the change
24 in VR-12 score between preoperative and postoperative assessments. Again, a multivariable regression
25 analysis will be performed to evaluate whether the development of postoperative delirium is an
26 independent predictor variable for the change in quality of life. POD will be entered as two categorical
27 variables: for incidence (present or absent) and for duration (<3 days POD or ≥3 days POD). The
28 following variables will be included in the model: age, sex, American Society of Anesthesiologists
29 physical score, Charlson co-morbidity index, type of surgery, randomization group, preoperative
30 depression, preoperative vascular disease, postoperative complications, cognitive function, composite
31 score on frailty tests and a history of falls. As above, we will use a model with backward elimination, to
32 avoid exclusion of predictors with suppressor effects. Previous work by our group has calculated the
33 minimal clinically important difference for overall VR-12 quality of life to be 1.4 for improvement and 3.6
34 for deterioration.[33]
35
36
37

38 For the above aims, we expect this study to be limited by loss to follow-up, estimated to be 50%. Those
39 lost to follow-up are likely to have more severe disease or deterioration in health. In order to determine
40 the influence of missing data in our analysis, we will also conduct a sensitivity analysis. We will calculate
41 the average cognition scores of those who declined. We will repeat the above models including missing
42 subjects, assuming all patients who did not participate had cognitive decline, quantified by the average
43 calculated from participants above. Additionally, to examine whether our sample selection method may
44 bias the results, we will compare baseline characteristics of those ENGAGES patients who were eligible
45 for our study to those who were not eligible.
46
47

48 Specific Aim 3: Explore whether patients who experience POD are more likely to become demented
49 within approximately one to two years of their surgery.
50

51 The primary endpoint of our analysis is incident dementia. A Cox proportional hazards regression will be
52 used to explore the likelihood of incident dementia associated with POD. POD will be entered as a
53 dichotomous variable (absent or present). The following variables will be included in the model: age,
54 sex, American Society of Anesthesiologists physical score, Charlson co-morbidity index, preoperative
55 cognitive function, type of surgery, randomization group, preoperative depression, preoperative
56 vascular disease, postoperative complications, and composite score on frailty tests and a history of falls.
57
58
59
60

1
2
3 All statistical analyses will be performed using SAS, version 9.4 (SAS Institute, Inc., Cary, North Carolina).
4 All other tests will be two-sided. By arbitrary convention all tests will be two-sided and considered
5 statistically significant at a $p < 0.05$, and all results will be presented with estimates and 95% confidence
6 intervals.
7

8 **Pre-specified additional analyses and sub-studies**

9
10 The primary aim of this study is to determine whether postoperative delirium predicts intermediate-
11 term cognitive impairment. However, as a sub-study of ENGAGES and SATISFY-SOS, several other
12 clinically relevant outcomes can be explored as well. SATISFY-SOS systematically collects detailed
13 information regarding patient centered outcomes, including patient perceived cognition. Correlation
14 between performance on neurocognitive testing and patient perceived cognition would be interesting
15 and useful clinically. Furthermore, the information regarding patients' characteristics will allow
16 exploration of risk factors for intermediate-term cognitive impairment. To investigate effects on
17 memory, we will perform a secondary analysis comparing the results of the SBT. Lastly, as part of
18 ENGAGES, some patients will have baseline NIH Toolbox cognitive testing, allowing description of long-
19 term cognitive trajectories as evaluated by these tests.
20
21
22

23 **Limitations**

24
25 This study contains several limitations. First, of most concern is the potential for non-response bias if
26 patients who do not participate are not a random subset of those contacted. We will attempt to
27 minimize the non-response rate by offering to visit patients at their homes if patients are unwilling to
28 come to the study center. We expect that those lost to follow-up would be more likely to have more
29 severe disease or health deterioration, potentially affecting cognitive function. We will thus conduct
30 appropriate sensitivity analyses to determine how missing outcomes data could alter the findings of our
31 study. Second, with an observational study, we cannot establish a causal relationship between
32 postoperative delirium and persistent declines in cognitive and quality of life. If an independent
33 relationship is found, we shall not be able to disambiguate whether postoperative delirium in some way
34 causes persistent decline in these outcomes, or whether it is a sign of underlying vulnerability. However,
35 since it is not possible to randomize patients to experience delirium, this limitation might be inevitable.
36 Third, since patients in this study are recruited from a single tertiary care center, the study sample may
37 not be representative of surgical patients in general. While these patients tend to have higher comorbid
38 disease burden than the general surgical population, including comorbidities in the statistical model will
39 account for these differences. Finally, while we have baseline cognitive assessments, we do not have
40 preoperative cognitive trajectories, and thus cannot determine whether the results of cognitive function
41 tests are a deviation from the pre-operative trend.
42
43
44
45
46
47

48 **Compliance**

49 **Subject Compliance**

50
51 The exposure of this study is post-operative delirium, so no monitoring of exposure compliance is
52 necessary. Methods to improve completion of one-year cognitive testing are described in Section 10.3,
53 "Limitations."
54
55

56 **Withdrawal of subjects**

1
2
3 Subjects may be withdrawn from the study only if requested by the patient. The reason for withdrawal
4 is recorded by the team's clinical project specialist.
5
6
7

8 **Ethical Considerations**

9
10 This study has been approved by the home institution's Institutional Review Board (IRB ID # 201407128).
11 Written, informed consent is obtained from all participants. As described in Section 7, "Study Groups,"
12 no special allowances are made for patients who are blind, deaf, illiterate or not fluent in English.
13 Participants may withdraw from the study at any time.
14
15

16 **Finance and Insurance**

17
18 Since this study involves only cognitive testing and surveys, it involves no more than minimal risk to the
19 patients. Finance details, insurance details, and cover for negligent and non-negligent harm are
20 therefore not relevant in this study.
21
22
23

24 **Reporting and Dissemination**

25
26 Results of this study will be published in a scientific journal. Participants will only be notified individually
27 if discoveries are made that directly impact their health. We intend to make deidentified individual
28 participant data used to obtain the results reported from this study available to researchers providing a
29 study proposal between three months and five years after article publication. This study protocol, the
30 statistical analysis plan and analytic code will also be available.
31
32
33
34

35 **Author Contributions**

36
37 Authorship for this study will be given to key personnel involved in study design, recruitment, data
38 collection and data analysis. There are no publication restrictions, and no professional writers will be
39 involved in the generation of the manuscript. MSA, AA, JZC, MM, RT, TW, EL are responsible for
40 conceptualizing study design. AA, JZC, RT, MM, HM, and AM were responsible for recruitment,
41 enrollment, data collection and editing the protocol. AA, JZC, and RT are responsible for drafting the
42 protocol. All authors including AA, JZC, MM, RT, AM, HM, NL, TW, EL, and MSA have critically revised the
43 protocol and approved the final version.
44
45
46
47
48

49 **Acknowledgement**

50 We thank Ms. Michelle Doering, a medical librarian at Becker Medical Library at Washington University
51 School of Medicine for developing the systemic search criteria.
52
53
54

55 **Competing Interests**

1
2
3 The authors and contributors have no competing interests to disclose.
4
5
6

7 **Grant Information**
8

9 Funding for this study was awarded by the Foundation for Anesthesia Education and Research (award
10 reference ID RFG-08/15/2016-Aranake-Chrisinger). Funding for the ENGAGES trial was through a
11 UH2/UH3 mechanism grant awarded by the National Institute on Aging (1UH2AG050312-01). Funding
12 for the SATISFY-SOS study was from a grant awarded by the Barnes-Jewish Hospital Foundation (7937-
13 77) and support provided by the Department of Anesthesiology at Washington University.
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

References

1. Bedford, P.D., *Adverse cerebral effects of anaesthesia on old people*. Lancet, 1955. **269**(6884): p. 259-63.
2. Moller, J.T., et al., *Long-term postoperative cognitive dysfunction in the elderly ISPOCD1 study. ISPOCD investigators. International Study of Post-Operative Cognitive Dysfunction*. Lancet, 1998. **351**(9106): p. 857-61.
3. Monk, T.G., et al., *Predictors of cognitive dysfunction after major noncardiac surgery*. Anesthesiology, 2008. **108**(1): p. 18-30.
4. Selnes, O.A., et al., *Cognition 6 years after surgical or medical therapy for coronary artery disease*. Ann Neurol, 2008. **63**(5): p. 581-90.
5. Avidan, M.S., et al., *Long-term cognitive decline in older subjects was not attributable to noncardiac surgery or major illness*. Anesthesiology, 2009. **111**(5): p. 964-70.
6. Dokkedal, U., et al., *Cognitive Functioning after Surgery in Middle-aged and Elderly Danish Twins*. Anesthesiology, 2016. **124**(2): p. 312-21.
7. *Projected Future Growth of the Older Population*. [cited 2016 02/22]; Available from: http://www.aoa.gov/AoARoot/Aging_Statistics/future_growth/future_growth.aspx - age.
8. Whitlock, E.L., A. Vannucci, and M.S. Avidan, *Postoperative delirium*. Minerva Anestesiol, 2011. **77**(4): p. 448-56.
9. Gottesman, R.F., et al., *Delirium after coronary artery bypass graft surgery and late mortality*. Ann Neurol, 2010. **67**(3): p. 338-44.
10. Koster, S., et al., *Consequences of delirium after cardiac operations*. Ann Thorac Surg, 2012. **93**(3): p. 705-11.
11. Bickel, H., et al., *High risk of cognitive and functional decline after postoperative delirium. A three-year prospective study*. Dement Geriatr Cogn Disord, 2008. **26**(1): p. 26-31.
12. Saczynski, J.S., et al., *Cognitive trajectories after postoperative delirium*. N Engl J Med, 2012. **367**(1): p. 30-9.
13. Jankowski, C.J., et al., *Cognitive and functional predictors and sequelae of postoperative delirium in elderly patients undergoing elective joint arthroplasty*. Anesth Analg, 2011. **112**(5): p. 1186-93.
14. Ballard, C., et al., *Optimised anaesthesia to reduce post operative cognitive decline (POCD) in older patients undergoing elective surgery, a randomised controlled trial*. PLoS One, 2012. **7**(6): p. e37410.
15. Abildstrom, H., et al., *Cognitive dysfunction 1-2 years after non-cardiac surgery in the elderly. ISPOCD group. International Study of Post-Operative Cognitive Dysfunction*. Acta Anaesthesiol Scand, 2000. **44**(10): p. 1246-51.
16. Cormack, F., et al., *A meta-analysis of cognitive outcome following coronary artery bypass graft surgery*. Neurosci Biobehav Rev, 2012. **36**(9): p. 2118-29.
17. Kat, M.G., et al., *Long-term cognitive outcome of delirium in elderly hip surgery patients. A prospective matched controlled study over two and a half years*. Dement Geriatr Cogn Disord, 2008. **26**(1): p. 1-8.
18. Inouye, S.K., et al., *The short-term and long-term relationship between delirium and cognitive trajectory in older surgical patients*. Alzheimers Dement, 2016. **12**(7): p. 766-75.
19. Gunther, M.L., et al., *The association between brain volumes, delirium duration, and cognitive outcomes in intensive care unit survivors: the VISIONS cohort magnetic resonance imaging study**. Crit Care Med, 2012. **40**(7): p. 2022-32.
20. Morandi, A., et al., *The relationship between delirium duration, white matter integrity, and cognitive impairment in intensive care unit survivors as determined by diffusion tensor imaging:*

- 1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
- the VISIONS prospective cohort magnetic resonance imaging study**. Crit Care Med, 2012. **40**(7): p. 2182-9.
21. Wacker, P., et al., *Post-operative delirium is associated with poor cognitive outcome and dementia*. Dement Geriatr Cogn Disord, 2006. **21**(4): p. 221-7.
 22. Lingehall, H.C., et al., *Preoperative Cognitive Performance and Postoperative Delirium Are Independently Associated With Future Dementia in Older People Who Have Undergone Cardiac Surgery: A Longitudinal Cohort Study*. Crit Care Med, 2017.
 23. Schenning, K.J., et al., *Surgery is associated with ventricular enlargement as well as cognitive and functional decline*. Alzheimers Dement, 2015.
 24. Abelha, F.J., et al., *Outcome and quality of life in patients with postoperative delirium during an ICU stay following major surgery*. Crit Care, 2013. **17**(5): p. R257.
 25. Kastaun, S., et al., *The Relevance of Postoperative Cognitive Decline in Daily Living: Results of a 1-Year Follow-up*. J Cardiothorac Vasc Anesth, 2016. **30**(2): p. 297-303.
 26. Wildes, T.S., et al., *Protocol for the Electroencephalography Guidance of Anesthesia to Alleviate Geriatric Syndromes (ENGAGES) study: a pragmatic, randomised clinical trial*. BMJ Open, 2016. **6**(6): p. e011505.
 27. Helsten, D.L., et al., *Methodologic Considerations for Collecting Patient-reported Outcomes from Unselected Surgical Patients*. Anesthesiology, 2016. **125**(3): p. 495-504.
 28. Bleck, T.P., et al., *What is the NIH toolbox, and what will it mean to neurology?* Neurology, 2013. **80**(10): p. 874-5.
 29. Weintraub, S., et al., *Cognition assessment using the NIH Toolbox*. Neurology, 2013. **80**(11 Suppl 3): p. S54-64.
 30. Carpenter, C.R., et al., *Four sensitive screening tools to detect cognitive dysfunction in geriatric emergency department patients: brief Alzheimer's Screen, Short Blessed Test, Ottawa 3DY, and the caregiver-completed AD8*. Acad Emerg Med, 2011. **18**(4): p. 374-84.
 31. Selim, A.J., et al., *Updated U.S. population standard for the Veterans RAND 12-item Health Survey (VR-12)*. Qual Life Res, 2009. **18**(1): p. 43-52.
 32. Xie, J., et al., *Survival times in people with dementia: analysis from population based cohort study with 14 year follow-up*. BMJ, 2008. **336**(7638): p. 258-62.
 33. Kronzer, V.L., et al., *Changes in quality of life after elective surgery: an observational study comparing two measures*. Qual Life Res, 2017. **26**(8): p. 2093-2102.

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.
Rothenhauser 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

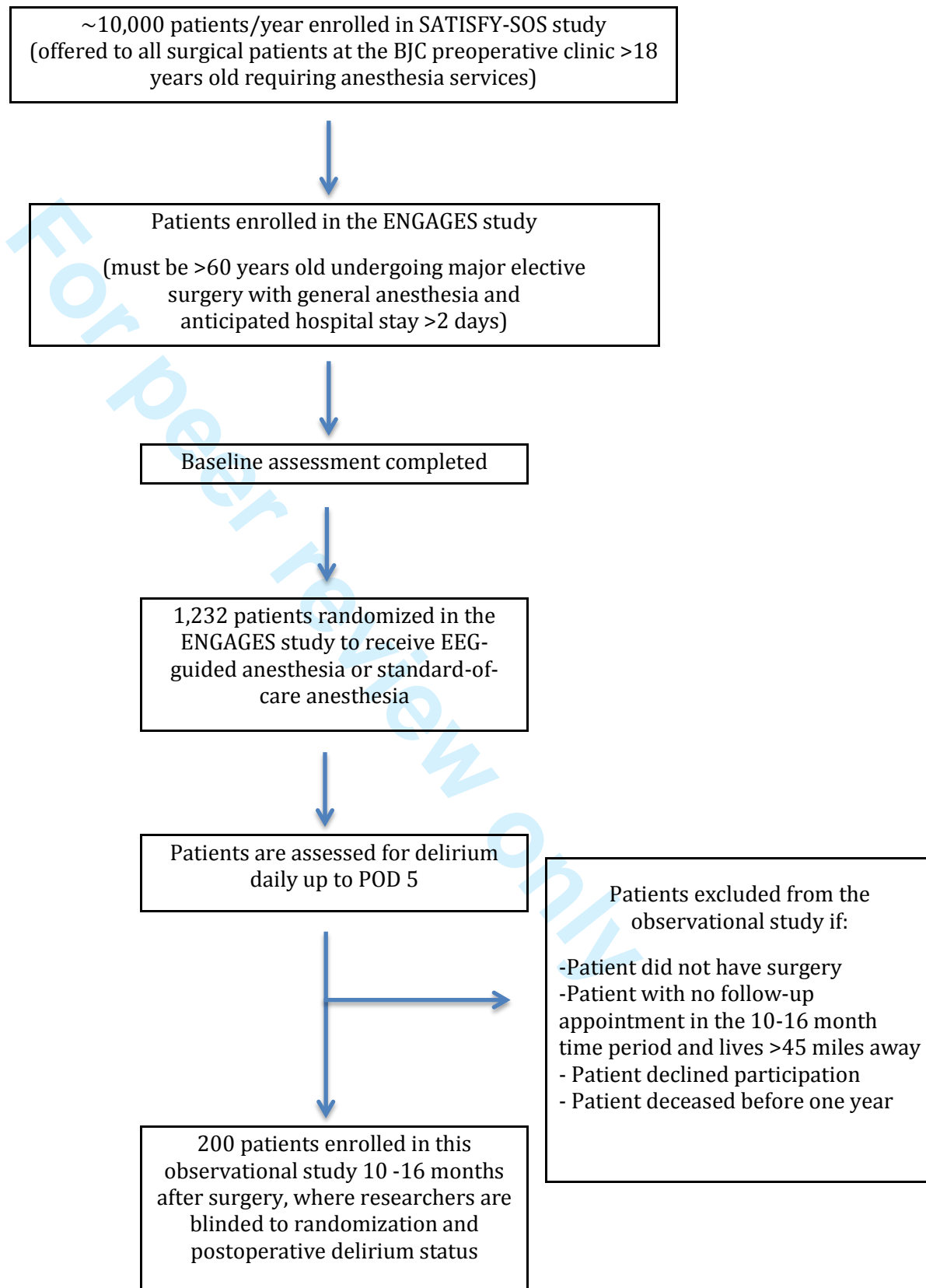
				mortality, hospital LOS, hospital discharge status, 1-year mortality rate, place of residence, recovery of ambulatory ability, and activities of daily living			recover level of ambulation, more likely to show a decline independence. No difference in postoperative complications, in-hospital mortality, 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

1. Tow, A., et al., *Cognitive Reserve and Postoperative Delirium in Older Adults*. J Am Geriatr Soc, 2016. **64**(6): p. 1341-6.
2. Neufeld, K.J., et al., *Long-Term Outcomes of Older Adults with and Without Delirium Immediately After Recovery from General Anesthesia for Surgery*. Am J Geriatr Psychiatry, 2015. **23**(10): p. 1067-74.
3. Sprung, J., et al., *Association of mild cognitive impairment with exposure to general anesthesia for surgical and nonsurgical procedures: a population-based study*. Mayo Clin Proc, 91 (2) (2016), pp. 208-217.
4. Hempenius, L., et al., *Long Term Outcomes of a Geriatric Liaison Intervention in Frail Elderly Cancer Patients*. PLoS One, 2016. **11**(2): p. e0143364.
5. Youngblom, E., et al., *The temporal relationship between early postoperative delirium and postoperative cognitive dysfunction in older patients: a prospective cohort study*. Can J Anaesth, 2014. **61**(12): p. 1084-92.
6. Hussain, M., et al., *General anesthetic and the risk of dementia in elderly patients: current insights*. Clin Interv Aging, 2014. **9**: p. 1619-28.
7. Abelha, F.J., et al., *Outcome and quality of life in patients with postoperative delirium during an ICU stay following major surgery*. Crit Care, 2013. **17**(5): p. R257.
8. Witlox, J., et al., *The neuropsychological sequelae of delirium in elderly patients with hip fracture three months after hospital discharge*. Int Psychogeriatr, 2013. **25**(9): p. 1521-31.
9. Radtke, F.M., et al., *Monitoring depth of anaesthesia in a randomized trial decreases the rate of postoperative delirium but not postoperative cognitive dysfunction*. Br J Anaesth, 2013. **110** Suppl 1: p. i98-105.

10. Saczynski, J.S., et al., *Cognitive trajectories after postoperative delirium*. N Engl J Med, 2012. **367**(1): p. 30-9.
11. Koster, S., et al., *Consequences of delirium after cardiac operations*. Ann Thorac Surg, 2012. **93**(3): p. 705-11.
12. Quinlan, N. and J.L. Rudolph, *Postoperative delirium and functional decline after noncardiac surgery*. J Am Geriatr Soc, 2011. **59 Suppl 2**: p. S301-4.
13. Wallbridge, H.R., et al., *Risk factors for postoperative cognitive and functional difficulties in abdominal aortic aneurysm patients: a three month follow-up*. Int J Geriatr Psychiatry, 2011. **26**(8): p. 818-24.
14. Jankowski, C.J., et al., *Cognitive and functional predictors and sequelae of postoperative delirium in elderly patients undergoing elective joint arthroplasty*. Anesth Analg, 2011. **112**(5): p. 1186-93.
15. Rudolph, J.L., et al., *Delirium: an independent predictor of functional decline after cardiac surgery*. J Am Geriatr Soc, 2010. **58**(4): p. 643-9.
16. Koster, S., A.G. Hensens, and J. van der Palen, *The long-term cognitive and functional outcomes of postoperative delirium after cardiac surgery*. Ann Thorac Surg, 2009. **87**(5): p. 1469-74.
17. Gogol, M., [Delirium in the elderly]. Z Gerontol Geriatr, 2008. **41**(6): p. 431-9.
18. Bickel, H., et al., *High risk of cognitive and functional decline after postoperative delirium. A three-year prospective study*. Dement Geriatr Cogn Disord, 2008. **26**(1): p. 26-31.
19. Kat, M.G., et al., *Long-term cognitive outcome of delirium in elderly hip surgery patients. A prospective matched controlled study over two and a half years*. Dement Geriatr Cogn Disord, 2008. **26**(1): p. 1-8.
20. Rudolph, J.L., et al., *Delirium is associated with early postoperative cognitive dysfunction*. Anaesthesia, 2008. **63**(9): p. 941-7.
21. Olofsson, B., et al., *Delirium is associated with poor rehabilitation outcome in elderly patients treated for femoral neck fractures*. Scand J Caring Sci, 2005. **19**(2): p. 119-27.
22. Rothenhausler, H.B., et al., *Psychiatric and psychosocial outcome of cardiac surgery with cardiopulmonary bypass: a prospective 12-month follow-up study*. Gen Hosp Psychiatry, 2005. **27**(1): p. 18-28.
23. Duppils, G.S. and K. Wikblad, *Cognitive function and health-related quality of life after delirium in connection with hip surgery. A six-month follow-up*. Orthop Nurs, 2004. **23**(3): p. 195-203.
24. Edelstein, D.M., et al., *Effect of postoperative delirium on outcome after hip fracture*. Clin Orthop Relat Res, 2004(422): p. 195-200.
25. Adunsky, A., et al., *The unfavorable nature of preoperative delirium in elderly hip fractured patients*. Arch Gerontol Geriatr, 2003. **36**(1): p. 67-74.
26. Lundstrom, M., et al., *Dementia after delirium in patients with femoral neck fractures*. J Am Geriatr Soc, 2003. **51**(7): p. 1002-6.
27. Edlund, A., et al., *Clinical profile of delirium in patients treated for femoral neck fractures*. Dement Geriatr Cogn Disord, 1999. **10**(5): p. 325-9.
28. Goldstein, M.Z., B.S. Fogel, and B.L. Young, *Effect of elective surgery under general anesthesia on mental status variables in elderly women and men: 10-month follow-up*. Int Psychogeriatr, 1996. **8**(1): p. 135-49.

Appendix B.

Patient Recruitment



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) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —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 <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	6-7
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —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) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	8-9

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

(e) Describe any sensitivity analyses

Continued on next page

For peer review only

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 (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	N/A
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time <i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure <i>Cross-sectional study</i> —Report numbers of outcome events or summary measures	N/A
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 (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	N/A
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.