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Title

Protocol for an observational study of delirium in the Post-Anesthesia Care Unit (PACU) as a potential predictor of subsequent postoperative delirium

Authors

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I. Abstract

Introduction: Postoperative delirium can be a serious consequence of major surgery, associated with longer hospital stays, readmission, cognitive and functional deterioration, and mortality. Delirium is an acute, reversible disorder characterized by fluctuating course, inattention, disorganized thinking, and altered level of consciousness. Delirium occurring in the hours immediately following anesthesia, and delirium occurring in the postoperative period of 1-5 days have been described as distinct clinical entities. This protocol describes an observational study with the aim of determining if delirium in the first hour following tracheal tube removal is a predictor of delirium in the five subsequent postoperative days. Improved understanding regarding the development of postoperative delirium would improve patient care and allow more effective implementation of delirium prevention measures.

Methods and analysis: Patients enrolled to the Electroencephalography Guidance of Anesthesia to Alleviate Geriatric Syndromes (ENGAGES) randomized controlled trial will be eligible for this sub-study. A validated delirium assessment method, the 3-minute Diagnostic Confusion Assessment Method (3D-CAM) and the Richmond Agitation and Sedation Scale (RASS) will be used to assess 100 patients for delirium at 30 minutes and 60 minutes following tracheal tube removal. Patients will also be assessed for delirium over postoperative days 1 to 5 using three validated methods, the Confusion Assessment Method (CAM), CAM for the Intensive Care Unit (CAM-ICU), and structured chart review. Logistic regression analysis will then be performed to test whether immediately postoperative delirium independently predicts subsequent postoperative delirium.

Ethics and dissemination: This observational sub-study of ENGAGES has been approved by the ethics board of Washington University School of Medicine. Enrollment began in June 2016 and will continue until June 2017. Dissemination plans include presentations at scientific conferences and scientific publications.

Registration: This protocol describes a sub-study of ENGAGES, which is registered at clinicaltrials.gov, NCT02241655 (last updated December 23, 2015).

II. Article summary

a. Strengths and limitations

Strengths:

- The 3-minute Diagnostic Confusion Assessment Method (3D-CAM) is a validated, appropriate method for assessment of delirium in the PACU or ICU patient population at multiple time points during their stay.
- Delirium assessments at 30 and 60 minutes after tracheal tube removal will allow serial evaluation of the development of delirium signs over the course of the immediate postoperative period

Limitations

- This sub-study is being conducted at only one academic medical center, Barnes-Jewish Hospital, and is a convenience sample based on surgical patients who have already consented to participation in the SATISFY-SOS study and ENGAGES trial.
- Patients may experience survey fatigue and be unwilling to complete 3D-CAM assessments at the 30 or 60 minute time points, or additional delirium assessments in postoperative days 1 to 5.
- The results of two types of delirium assessments will be compared in order to determine whether delirium in the first hour following tracheal tube removal is a predictor of delirium in the five subsequent postoperative days.

III. Introduction

a. Background and rationale

The following protocol is compliant with published guidelines for observational study protocols (1). This study intends to answer the research question of whether delirium in the first hour post-tracheal tube removal, assessed in the post-anesthesia care unit (PACU) or intensive care unit (ICU), is independently predictive of delirium on postoperative days 1 to 5.

Delirium is an acute, reversible disorder of attention, cognition and level of consciousness (2). Postoperative delirium is a serious and common complication of major surgery, especially for older patients. Postoperative delirium is associated with longer hospital stays, readmission, cognitive deterioration, morbidity, and mortality. Accurate assessment for delirium during the postoperative recovery period might help guide decision-making for treatment and rehabilitation in order to prevent negative outcomes.

It is common practice for patients to be admitted to a PACU or ICU following completion of surgery. Patients are observed in the PACU until an attending physician determines that they are discharge-ready, according to specific criteria, such as activity, respiration, circulation, consciousness, and color, as elaborated in the Aldrete score (3). Approximately 80% of patients at our hospital are eligible for PACU discharge between 1 hour and 3 hours after PACU admission (4). During the first 3 postoperative hours, a large number of patients present with delirium, more commonly of the hypoactive type than of the hyperactive type. Especially in cases of hyperactivity, postoperative delirium can have direct consequences, as patients may fall from their beds; attempt urine catheter extraction, intravenous line removal, or tracheal tube withdrawal; and cause injuries to themselves or to staff (5). In a study of 400 patients conducted by Card et al., 124 patients (31%) displayed signs of delirium at PACU admission, and 65 patients (16%) had delirium signs during their PACU stay (6). Delirium presenting in the PACU has been referred to as “emergence delirium” and may be attributable to residual effects

of general anesthesia, and should theoretically resolve within minutes to hours. Postoperative delirium, arbitrarily defined as occurring 1 to 5 days following surgery, may have distinct etiologies from emergence delirium in the PACU. The relationship between delirium occurring immediately following surgery and emergency from anesthesia and postoperative delirium after the day of surgery is currently not known.

Several studies have suggested an association between emergence delirium, manifesting in the PACU, and postoperative delirium, manifesting after the day of surgery (6–9). However, these studies each employed different methods for assessing emergence delirium. Card et al. used the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) for identifying patients with delirium, and the Richmond Agitation-Sedation Scale (RASS) to classify the delirium as hyper or hypoactive (6,10–12). This study found that of the 16% of subjects found to have delirium signs during their PACU stay, when assessed at 30min, 60min, and at discharge, 92% exhibited signs of the hypoactive subtype and 8% exhibited signs of the hyperactive subtype (6). This is compared to the findings at time of PACU admission when 31% of patients had signs of delirium of which, 56% exhibited signs of the hypoactive subtype and 44% exhibited signs of the hyperactive subtype (6). A study of 91 patients conducted by Neufeld et al. using psychiatrist evaluation based on DSM4 criteria found a 45% prevalence of delirium in the PACU (8). Out of 19 episodes of postoperative delirium found, 14 (74%) had experienced emergence delirium while in the PACU (8). Using the Nu-DESC assessment for delirium, a cumulative observational scoring system including disorientation, inappropriate behavior, inappropriate communication, illusions/hallucinations, and psychomotor retardation, assessed in three time periods for a total of 12 hours, Radtke et al. observed an 11% prevalence of emergence delirium in the PACU (7). Of 38 patients who experienced delirium in the first postoperative day (38/862 = 4.2%), 32 (84.2%) had previously displayed emergence delirium (7). In their population of 47 hip-fracture repair patients, Sharma et al. employed the unabbreviated Confusion Assessment Method (CAM) assessment at 60 minutes after discontinuation of isoflurane and found a prevalence of emergence delirium of 45%. Of these patients, 36% subsequently experienced postoperative delirium, and delirium in the PACU was a strong predictor of subsequent postoperative delirium, according to a Fisher's Exact Test ($P < 0.001$) with 100% sensitivity and 85% specificity. (9).

The Confusion Assessment Method (CAM) is a validated and widely-used delirium assessment instrument that is used primarily by non-psychiatrists (13). Both the CAM-ICU and the 3-minute Diagnostic Confusion Assessment Method (3D-CAM) are abbreviated delirium assessments derived from the CAM, with the CAM-ICU designed specifically for assessing intubated or nonverbal patients (11,12). The 3D-CAM consists of a subset of the assessment components used in the CAM, designed to only take 3 minutes, supplemented by a series of questions regarding patient behavior during the interview to be completed by the interviewer following the patient visit (11). The major advantage of both the 3D-CAM and CAM-ICU compared to the unabbreviated CAM are the assessments' relative brevity.

The 3D-CAM and CAM-ICU require similar time to complete. A previous study comparing related methods of delirium assessment estimated sensitivity of 93% and specificity of 96% for the 3D-CAM in detecting delirium in patients without dementia as compared to the CAM (11). A study comparing the 3D-CAM and CAM-ICU directly in a general medicine patient population aged >75 found a 95% sensitivity for the 3D CAM [95% CI 74-100%] and a 53% sensitivity for the CAM-ICU [95% CI 29-76%] (14). The 3D-CAM and CAM-ICU were both reported as having >90% specificity for detecting delirium (14). Unlike the CAM-ICU, the 3D-CAM requires the patient to verbally answer questions assessing for orientation and attention. These features are emphasized in the DSM-V over altered level of consciousness, which the CAM-ICU assesses by incorporating the RASS score into its delirium assessment (11). In this study, the 3D-CAM is chosen over the CAM-ICU its higher sensitivity in detecting delirium in verbal patients.

b. Specific aims

Aim 1

This study aims to determine if delirium in the first hour post-tracheal tube removal is predictive of delirium in the five subsequent postoperative days.

We hypothesize that delirium in the first hour post-tracheal tube removal is independently predictive of delirium manifesting during postoperative days 1-5.

c. Significance

Postoperative delirium is a serious complication in patients who have undergone major surgery, especially among the older population. Improved understanding regarding the development of early-onset delirium and its association with delirium in the postoperative period can inform and improve patient care, with the goal of reducing delirium and its consequences.

IV. Methods and analysis

a. Study design

This retrospective study is a sub-study of both the Electroencephalography Guidance of Anesthesia to Alleviate Geriatric Syndromes Study (ENGAGES, NCT02241655) and the Systematic Assessment and Targeted Improvement of Services Following Yearlong Surgical Outcomes Surveys Study (SATISFY-SOS, NCT02032030), being conducted at Washington University. ENGAGES is a randomized clinical trial to determine whether EEG-guided anesthesia care can reduce the incidence of postoperative delirium and improve health-related quality of life postoperatively, when compared to usual anesthesia care. SATISFY-SOS is an ongoing cohort study that is obtaining detailed information on unselected surgical patients, and is tracking their health and well-being in the intermediate term postoperatively. All members of the ENGAGES trial are also

enrolled in SATISFY-SOS, and the patients included in the current study will be comprised of ENGAGES participants only.

i. Delirium assessment method

The primary outcome in this study is the presence of delirium in the immediate postoperative period, within 1 hour following tracheal tube removal after the completion of surgery.

Only patients who are not delirious prior to surgery are enrolled in the ENGAGES trial. As stated in the SATISFY-SOS consent, patients can be assessed for delirium up to two times per day. In this sub-study, 3D-CAM assessments will be performed in the PACU or ICU at 30 minutes and at 1 hour following tracheal tube removal. The presence of delirium in the first hour will be defined as a positive 3D-CAM assessment at either of these two time points. The characteristics of 1) acute onset/fluctuating course, 2) inattention, and 3) disorganized thinking OR altered level of consciousness must be observed in the patient based on information gathered during the 3D-CAM assessment for delirium to be considered present. Should a patient decline participation in the 3D-CAM at a given time point, researchers will still ask that patient to participate at any remaining time point in the study.

All assessments will be performed by individuals rigorously trained in both the full CAM assessment and 3D-CAM assessment.

All procedures in this study will be conducted in the same manner for patients in either the ICU or the PACU. Staff in the PACUs and the ICUs will be informed of the purpose and the procedures of the study.

ii. Sample size

We base our sample size calculations on the unadjusted relationship between PACU delirium and postoperative delirium found in a prior study. This study found the crude odds ratio to be approximately 3.9 (6). Since our first hour after tracheal tube removal delirium measurements and postoperative delirium measurements occur in the same patient, we use the McNemar test for dependent pairs. Conservatively assuming an odds ratio of 3.0, along with 80% power and α of 0.05, two tails, and 30% discordant pairs (6), the required sample size is 100 patients. Assuming 10% of patients are unable to be assessed, we will enroll 110 patients.

iii. Blinding

Researchers responsible for performing delirium assessments in the ICU and PACU as part of this study will be blinded from the patient's group status in the ENGAGES study and will not participate in intraoperative monitoring, postoperative assessments in the first five postoperative days, or delirium chart review. 3D-CAM assessments performed

in this study will be reviewed and entered into the REDCap database by a second researcher to ensure accuracy in the delirium assessment.

Assessors of delirium in the postoperative period and in the delirium chart review for the ENGAGES study will be blinded from the results of delirium assessments performed in the ICU and PACU as part of this study.

b. Study group and consenting process

The target population for this study comprises all patients undergoing elective surgery at Barnes Jewish Hospital beginning June 8, 2016 and until the study enrollment goal of 100 assessed patients is reached. Patients who consent to participation in both the SATISFY-SOS and ENGAGES studies are eligible for this study. Patients may choose to refuse participation in this study at any time point.

We note that not all patients undergoing surgical procedures at Barnes Jewish Hospital will have the opportunity to participate in this study.

i. Eligibility criteria

Inclusion criteria:

In order to be included in this study, patients must be:

(i) Enrolled in the SATISFY-SOS study or ENGAGES study (Appendix A);
(ii) Tracheal tube removal on postoperative day 0 before 7pm.

c. Data

The following are the types of data that we anticipate using in this study. These parameters have significant overlap with the data already being collected on patients enrolled in ENGAGES.

We will collect the following patient baseline characteristics: age, sex, race, smoking history, alcohol history, dementia, pre-existing medical or surgical conditions, preoperative medications (including benzodiazepines, antidepressants, neuroleptics, analgesics), previous surgical procedures in the last 3 months. For our analysis, we will be calculating each patient's Charlson Comorbidity Index score and their score on the Short Blessed Test.

We will collect the following data regarding patient surgery: type of surgery, duration of surgery, duration of anesthesia, anesthesia protocol and dose, time of tracheal tube removal, complications or adverse events.

The primary outcome in this study is the presence of delirium During the PACU or ICU stay, delirium assessments using the 3D-CAM will be performed at 30 minutes and at

60 minutes following tracheal tube removal in either the PACU or ICU. If an eligible patient is approached but unable to or declines to participate in the study at either or both time points, the reason(s) for the non-assessment will be recorded. We anticipate reasons for non-assessment to include logistical barrier to approach patient, patient inability to complete the verbal assessment, and active decline to participate by the patient. Patients are considered incapable of verbal communication and completion of delirium assessment at that time if they do not express themselves verbally to any prompt or stimulus. Information regarding the length of stay in PACU or ICU, RASS score at both time points, nurse reports, adverse events, or interventions will also be collected.

Data regarding the postoperative period will also be collected from the ENGAGES database: daily CAM assessments performed according to the ENGAGES protocol, which states that delirium will be diagnosed by a combination of CAM assessments, the full CAM or the CAM-ICU, and the delirium chart review, where a researcher blinded to the CAM/CAM-ICU results will do a comprehensive chart review to detect any incidences of delirium and identify postoperative medications, duration of hospital stay, nurse reports, adverse events, or additional interventions.

All electronic data collected in the course of this study, as well as the SATISFY-SOS and ENGAGES databases, are hosted on a firewall-secured network server. This server is managed and maintained by the IT team of the Department of Anesthesiology, and is securely housed behind two locked doors in the departmental offices. The project Informaticist, Data Manager, and Director(s) are the only individuals with full access to these password-protected and encrypted databases. Delirium assessments performed in the ICU and PACU are completed using paper surveys and are securely stored within the department and their results are entered into a REDCap database.

i. Statistical considerations

First, we will calculate the crude association between delirium within the first hour after tracheal tube removal and postoperative delirium using the McNemar test for two dependent variables.

Multivariable logistic regression will be performed with the presence of delirium in the postoperative period as the dependent variable and the presence of delirium as detected in the PACU or ICU by positive 3D-CAM, which is the principle type of data collected in this study, will serve as the independent variable of interest. We assume a 25% prevalence of postoperative delirium within the first hour following tracheal tube removal in our study population based on previous studies (15,16). With 100 assessed patients, the model would have a sufficient number of outcome events (25) to include early delirium within the first hour after tracheal tube removal along with three confounders, assuming 6 outcome events are needed per variable (17). The three confounders that will be included in the model are age (continuous), Short Blessed Test (continuous) (18,19), and Charlson Comorbidity Index (continuous) (20,21). Age of 65 years or older, cognitive impairment, dementia, and coexisting medical conditions

including multiple comorbidities, chronic renal or hepatic disease, stroke, and neurologic have been consistently described as risk factors for postoperative delirium (22). We will perform additional sensitivity analyses using the assumptions that 1) active patient decline of delirium assessment and 2) inability to give verbal responses represent postoperative delirium in the first hour following tracheal tube removal in those patients.

Additional analyses may be performed *post-hoc* with the descriptive data collected through the ENGAGES and SATISFY-SOS databases if they are believed to contain significant confounders.

Coefficients to variables will be considered significant at level of α<0.05. Results will be reported as odds ratios with 95% confidence intervals. We pre-specify the minimum important odds ratio for having potential predictive utility would be a >20% change in either direction (i.e. OR < 0.8 or > 1.2) (23). The 3D-CAM is less sensitive than the CAM for delirium detection (11). Therefore, it is possible that some episodes of delirium in the PACU or ICU will not be detected with the 3D-CAM. This increases the possibility that our study will not detect an association between delirium in the PACU or ICU and postoperative delirium even if such an association is present (i.e., false negative result).

d. Anticipated results

We anticipate that the presence of delirium in the first hour post-tracheal tube removal will be identified as an independent predictor of delirium later on in the postoperative period.

e. Strengths and limitations

i. Strengths

We believe that the 3D-CAM is an appropriate method of assessing for delirium in the PACU or ICU patient population at multiple time points during their stay. Previous studies have suggested that the 3D-CAM has high sensitivity and specificity in detecting delirium, and greater sensitivity when compared to the CAM-ICU (9,11,14).

Performing two brief assessments for delirium at time points 30 and 60 minutes after tracheal tube removal has several advantages. It will allow the assessment of delirium to be more accurate in each patient, increase the likelihood of completing at least one assessment per patient, and track the development of delirium signs over the course of the immediate postoperative period.

ii. Limitations

This study has several limitations. It is being conducted at only one academic medical center, Barnes-Jewish Hospital. The sample is a convenience sample based on surgical patients who have already consented to participation in SATISFY-SOS study and the ENGAGES trial.

We foresee limitations regarding our capacity to accurately monitor tracheal tube removal times, though we will work with PACU and ICU staff in order to communicate effectively and approach patients at our desired time intervals after tracheal tube removal. Researchers will ensure that delirium assessments are performed as close to 30 minutes and 60 minutes post-tracheal tube removal as possible. However, due to logistical considerations such as patient transport and Anesthesia team handoff, patients may not be available to approach for delirium at either time point.

We anticipate that a significant proportion of patients may be unwilling to participate in the 3D-CAM during their stay in the PACU or ICU. For example, many more patients may elect to complete a single 3D-CAM at 30 minutes post-tracheal tube removal rather than at both time points. Patient responses to the 3D-CAM administered at the 2nd time point may also be influenced by their 3D-CAM at 30 minutes after tracheal tube removal; i.e. they may experience survey fatigue. It is also possible that participation in this study may impact a patient's willingness to continue their enrollment in ENGAGES, including the completion of the full CAM in the first five postoperative days and other types of data collected in ENGAGES.

It is not ideal to compare incidence of emergence delirium as assessed by 3D-CAM in the PACU or ICU with delirium incidence assessed by the unabbreviated CAM, CAM-ICU, or delirium chart review in the postoperative period. While the CAM is a validated instrument for detection of delirium by non-psychiatrists, it does take much longer to administer. As it will be advantageous for this study to assess for delirium at two different time points in a relatively short period, we feel that the advantages of using the 3D-CAM outweigh the possible losses in sensitivity and specificity that will result from departure from the full CAM.

f. Compliance

As this is an observational study, no procedures for monitoring exposure compliance are necessary. Patients may be withdrawn from this study, as well as SATISFY-SOS, or ENGAGES if requested. As described in the consent forms for SATISFY-SOS and ENGAGES, data already collected may continue to be used.

V. Ethical considerations

We have considered the burden imposed on patients having to undergo two successive 3D-CAM assessments in the first hour after tracheal tube removal. As the 3D-CAM is very limited in duration, usually requiring patient participation for 3 minutes (9), we believe the selection of this assessment method is acceptable. We do not believe that participation in the 3D-CAM up to 2 times during PACU or ICU stay will have any negative effects on patient care or postoperative outcomes.

This study has received institutional IRB approval at Washington University School of Medicine IRB ID#201612007 on December 8, 2016.

a. Finance and insurance

This study involves little-to-no risk to patients, and patients will not be compensated for participation. There are no relevant finance details, insurance details, or covers for negligent and non-negligent harm in this study.

b. Reporting and dissemination

Results of this study will be presented at national meetings and published in a scientific journal. Participants will not be individually notified regarding the results of this study.

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VII. Author contributions

VC and CMT contributed equally to study conceptualization, statistical design, protocol drafting, and protocol editing.
VLK contributed to statistical design.
SLM completed the institutional IRB approval process.
MSA contributed to study conceptualization and protocol editing.

VIII. Collaborators

The authors thank Jamila Burton, Daniel Emmert, Thomas Graetz, Shelly Gupta, Tony Lee, Hannah Maybrier, Angela Mickle, Maxwell Muench, Jordan Oberhaus, Ben Palanca, Aamil Patel, James Spencer, Chloe Stallion, Tracey Stevens, Brian Torres, Emma Trammel, Ravi Upadhyayula, and Troy Wildes.

IX. Funding information

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X. Data Sharing

Data collection for this study is ongoing.

XI. Competing interests

The authors report no conflicts of interest in conducting this study.

XII. Appendix A

a. ENGAGES Inclusion and Exclusion Criteria

Inclusion:

1. Adults older than 60;
2. competent to provide informed consent;
3. undergoing major elective surgery requiring a minimum stay of 2 days postoperatively (e.g., major open cardiac, thoracic, vascular, intra-abdominal, gynecologic, urologic, orthopedic, hepato-biliary and ear, nose and throat surgery);
4. enrolled in the SATISFY-SOS study

Exclusion:

1. Unable to provide informed consent;
2. undergoing neurosurgical procedures;
3. preoperative delirium;
4. unable to participate adequately in delirium screening including those who are blind, deaf, illiterate or not fluent in English;
5. history of intraoperative awareness;
6. additional surgery planned within five days of index surgery

b. SATISFY-SOS Inclusion and Exclusion Criteria

Inclusion:

1. Surgical and procedural patients who require anesthesia services

Exclusion:

1. Patients under the age of 18 years

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***
Title: **Protocol for an observational study of delirium in the Post-Anesthesia Care Unit (PACU) as a potential predictor of subsequent postoperative delirium**

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract **Complete**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **Complete**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **Complete**
Objectives	3	State specific objectives, including any prespecified hypotheses **Complete**
Methods		
Study design	4	Present key elements of study design early in the paper **Complete**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **Complete**
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants **Complete**
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **Complete**
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 **Complete**
Bias	9	Describe any efforts to address potential sources of bias **Complete**
Study size	10	Explain how the study size was arrived at **Complete**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **Complete**
Statistical methods	12	**Complete**
		(*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*) If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses
Results		
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 **Complete**

		(b) Give reasons for non-participation at each stage **Complete**
		(c) Consider use of a flow diagram **Complete**
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **Complete**
		(b) Indicate number of participants with missing data for each variable of interest **Data collection ongoing**
Outcome data	15*	Report numbers of outcome events or summary measures **Data collection ongoing**
Main results	16	**Data collection ongoing** (*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
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **Data collection ongoing**
Discussion		**Data collection ongoing**
Key results	18	Summarise key results with reference to study objectives
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
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
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 **Complete**

*Give information separately for exposed and unexposed groups.

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.

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Protocol for an observational study of delirium in the Post-Anesthesia Care Unit (PACU) as a potential predictor of subsequent postoperative delirium

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Title

Protocol for an observational study of delirium in the Post-Anesthesia Care Unit (PACU) as a potential predictor of subsequent postoperative delirium

Authors

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I. Abstract

Introduction: Postoperative delirium can be a serious consequence of major surgery, associated with longer hospital stays, readmission, cognitive and functional deterioration, and mortality. Delirium is an acute, reversible disorder characterized by fluctuating course, inattention, disorganized thinking, and altered level of consciousness. Delirium occurring in the hours immediately following anesthesia, and delirium occurring in the postoperative period of 1-5 days have been described as distinct clinical entities. This protocol describes an observational study with the aim of determining if delirium in the first hour following tracheal tube removal is a predictor of delirium in the five subsequent postoperative days. Improved understanding regarding the development of postoperative delirium would improve patient care and allow more effective implementation of delirium prevention measures.

Methods and analysis: Patients enrolled to the Electroencephalography Guidance of Anesthesia to Alleviate Geriatric Syndromes (ENGAGES) randomized controlled trial will be eligible for this sub-study. A validated delirium assessment method, the 3-minute Diagnostic Confusion Assessment Method (3D-CAM) and the Richmond Agitation and Sedation Scale (RASS) will be used to assess 100 patients for delirium at 30 minutes and 60 minutes following tracheal tube removal. Patients will also be assessed for delirium over postoperative days 1 to 5 using three validated methods, the Confusion Assessment Method (CAM), CAM for the Intensive Care Unit (CAM-ICU), and structured chart review. Logistic regression analysis will then be performed to test whether immediately postoperative delirium independently predicts subsequent postoperative delirium.

Ethics and dissemination: This observational sub-study of ENGAGES has been approved by the ethics board of Washington University School of Medicine. Enrollment began in June 2016 and will continue until June 2017. Dissemination plans include presentations at scientific conferences and scientific publications.

Registration: This protocol describes a sub-study of ENGAGES, which is registered at clinicaltrials.gov, NCT02241655 (last updated December 23, 2015).

II. Article summary

a. Strengths and limitations

Strengths:

- The 3-minute Diagnostic Confusion Assessment Method (3D-CAM) is a validated, appropriate method for assessment of delirium in the PACU or ICU patient population at multiple time points during their stay.
- Delirium assessments at 30 and 60 minutes after tracheal tube removal will allow serial evaluation of the development of delirium signs over the course of the immediate postoperative period

Limitations

- This sub-study has a relatively small sample size, is being conducted at only one academic medical center, Barnes-Jewish Hospital, and is a convenience sample based on surgical patients who have already consented to participation in the SATISFY-SOS study and ENGAGES trial.
- Patients may experience survey fatigue and be unwilling to complete 3D-CAM assessments at the 30 or 60 minute time points, or additional delirium assessments in postoperative days 1 to 5.
- The results of two types of delirium assessments will be compared in order to determine whether delirium in the first hour following tracheal tube removal is a predictor of delirium in the five subsequent postoperative days.

III. Introduction

a. Background and rationale

The following protocol is compliant with published guidelines for observational study protocols (1). This study intends to answer the research question of whether delirium in the first hour post-tracheal tube removal, assessed in the post-anesthesia care unit (PACU) or intensive care unit (ICU), is independently predictive of delirium on postoperative days 1 to 5.

Delirium is an acute, reversible disorder of attention, cognition and level of consciousness (2). Postoperative delirium is a serious and common complication of major surgery, especially for older patients. Postoperative delirium is associated with longer hospital stays, readmission, cognitive deterioration, morbidity, and mortality. Accurate assessment for delirium during the postoperative recovery period might help guide decision-making for treatment and rehabilitation in order to prevent negative outcomes.

It is common practice for patients to be admitted to a PACU or ICU following completion of surgery. Patients are observed in the PACU until an attending physician determines that they are discharge-ready, according to specific criteria, such as activity, respiration, circulation, consciousness, and color, as elaborated in the Aldrete score (3). Approximately 80% of patients at our hospital are eligible for PACU discharge between 1 hour and 3 hours after PACU admission (4). During the first 3 postoperative hours, a large number of patients present with delirium, more commonly of the hypoactive type than of the hyperactive type. Especially in cases of hyperactivity, postoperative delirium can have direct consequences, as patients may fall from their beds; attempt urine catheter extraction, intravenous line removal, or tracheal tube withdrawal; and cause injuries to themselves or to staff (5). In a study of 400 patients conducted by Card et al., 124 patients (31%) displayed signs of delirium at PACU admission, and 65 patients (16%) had delirium signs during their PACU stay (6). Delirium presenting in the PACU has been referred to as “emergence delirium” and may be attributable to residual effects

of general anesthesia, and should theoretically resolve within minutes to hours. Postoperative delirium, arbitrarily defined as occurring 1 to 5 days following surgery, may have distinct etiologies from emergence delirium in the PACU. The relationship between delirium occurring immediately following surgery and emergency from anesthesia and postoperative delirium after the day of surgery is currently not known.

Several studies have suggested an association between emergence delirium, manifesting in the PACU, and postoperative delirium, manifesting after the day of surgery (6–9). However, these studies each employed different methods for assessing emergence delirium. Card et al. used the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) for identifying patients with delirium, and the Richmond Agitation-Sedation Scale (RASS) to classify the delirium as hyper or hypoactive (6,10–12). This study found that of the 16% of subjects found to have delirium signs during their PACU stay, when assessed at 30min, 60min, and at discharge, 92% exhibited signs of the hypoactive subtype and 8% exhibited signs of the hyperactive subtype (6). This is compared to the findings at time of PACU admission when 31% of patients had signs of delirium of which, 56% exhibited signs of the hypoactive subtype and 44% exhibited signs of the hyperactive subtype (6). A study of 91 patients conducted by Neufeld et al. using psychiatrist evaluation based on DSM4 criteria found a 45% prevalence of delirium in the PACU (8). Out of 19 episodes of postoperative delirium found, 14 (74%) had experienced emergence delirium while in the PACU (8). Using the Nu-DESC assessment for delirium, a cumulative observational scoring system including disorientation, inappropriate behavior, inappropriate communication, illusions/hallucinations, and psychomotor retardation, assessed in three time periods for a total of 12 hours, Radtke et al. observed an 11% prevalence of emergence delirium in the PACU (7). Of 38 patients who experienced delirium in the first postoperative day (38/862 = 4.2%), 32 (84.2%) had previously displayed emergence delirium (7). In their population of 47 hip-fracture repair patients, Sharma et al. employed the unabbreviated Confusion Assessment Method (CAM) assessment at 60 minutes after discontinuation of isoflurane and found a prevalence of emergence delirium of 45%. Of these patients, 36% subsequently experienced postoperative delirium, and delirium in the PACU was a strong predictor of subsequent postoperative delirium, according to a Fisher's Exact Test ($P < 0.001$) with 100% sensitivity and 85% specificity. (9).

The Confusion Assessment Method (CAM) is a validated and widely-used delirium assessment instrument that is used primarily by non-psychiatrists (13). Both the CAM-ICU and the 3-minute Diagnostic Confusion Assessment Method (3D-CAM) are abbreviated delirium assessments derived from the CAM, with the CAM-ICU designed specifically for assessing intubated or nonverbal patients (11,12). The 3D-CAM consists of a subset of the assessment components used in the CAM, designed to only take 3 minutes, supplemented by a series of questions regarding patient behavior during the interview to be completed by the interviewer following the patient visit (11). The major advantage of both the 3D-CAM and CAM-ICU compared to the unabbreviated CAM are the assessments' relative brevity.

The 3D-CAM and CAM-ICU require similar time to complete. A previous study comparing related methods of delirium assessment estimated sensitivity of 93% and specificity of 96% for the 3D-CAM in detecting delirium in patients without dementia as compared to the CAM (11). A study comparing the 3D-CAM and CAM-ICU directly in a general medicine patient population aged >75 found a 95% sensitivity for the 3D CAM [95% CI 74-100%] and a 53% sensitivity for the CAM-ICU [95% CI 29-76%] (14). The 3D-CAM and CAM-ICU were both reported as having >90% specificity for detecting delirium (14). Unlike the CAM-ICU, the 3D-CAM requires the patient to verbally answer questions assessing for orientation and attention. These features are emphasized in the DSM-V over altered level of consciousness, which the CAM-ICU assesses by incorporating the RASS score into its delirium assessment (11). In this study, the 3D-CAM is chosen over the CAM-ICU its higher sensitivity in detecting delirium in verbal patients.

A strong association between emergence delirium as occurring in the PACU and delirium in the post-operative period would suggest the need for changes or additions to the standard of care for patients in the PACU. These changes could include delirium prevention methods, reliable identification of patients presenting with delirium, and prompt treatment of delirium.

Several interventions have been previously shown to reduce the rates of delirium developing during hospital care: regular orienting of patients to time and surroundings, reducing visual and auditory sensory deficits, maintaining adequate nutrition and fluids, ensuring adequate environment for sleep, encouraging mobility, and reducing use of medical restraints (2). Identification of delirium can be facilitated with the use of validated bedside screening methods such as the 3D-CAM or CAM-ICU by non-psychiatrist healthcare personnel. Non-pharmacological measures such as reorientation, correction of sensory deficits, providing a calm patient-care setting with fewer disturbances, and encouraging adequate sleep are preferred over the use of medications to treat acute delirium (2)

Signs of delirium such as fluctuating level of consciousness and disorganized thinking should not be considered as part of the “normal” course for patients in the PACU. Instead, healthcare teams should integrate these findings into their care of patients and in recommendations given with patient hand-off following PACU stay. These findings should be considered when addressing each patient’s pain, analgesia regimen, sedation, and target sedation score as part of a tailored delirium treatment regimen(15).

b. Specific aims

Aim 1

This study aims to determine if delirium in the first hour post-tracheal tube removal is predictive of delirium in the five subsequent postoperative days.

We hypothesize that delirium in the first hour post-tracheal tube removal is independently predictive of delirium manifesting during postoperative days 1-5.

c. Significance

Postoperative delirium is a serious complication in patients who have undergone major surgery, especially among the older population. Improved understanding regarding the development of early-onset delirium and its association with delirium in the postoperative period can inform and improve patient care, with the goal of reducing delirium and its consequences.

IV. Methods and analysis

a. Study design

This retrospective study is a sub-study of both the Electroencephalography Guidance of Anesthesia to Alleviate Geriatric Syndromes Study (ENGAGES, NCT02241655) and the Systematic Assessment and Targeted Improvement of Services Following Yearlong Surgical Outcomes Surveys Study (SATISFY-SOS, NCT02032030), being conducted at Washington University. ENGAGES is a randomized clinical trial to determine whether EEG-guided anesthesia care can reduce the incidence of postoperative delirium and improve health-related quality of life postoperatively, when compared to usual anesthesia care. SATISFY-SOS is an ongoing cohort study that is obtaining detailed information on unselected surgical patients, and is tracking their health and well-being in the intermediate term postoperatively. All members of the ENGAGES trial are also enrolled in SATISFY-SOS, and the patients included in the current study will be comprised of ENGAGES participants only.

i. Delirium assessment method

The primary outcome in this study is the presence of delirium in the immediate postoperative period, within 1 hour following tracheal tube removal after the completion of surgery.

Only patients who are not delirious prior to surgery are enrolled in the ENGAGES trial. As stated in the SATISFY-SOS consent, patients can be assessed for delirium up to two times per day. In this sub-study, 3D-CAM assessments will be performed in the PACU or ICU at 30 minutes and at 1 hour following tracheal tube removal. The presence of delirium in the first hour will be defined as a positive 3D-CAM assessment at either of these two time points. The characteristics of 1) acute onset/fluctuating course, 2) inattention, and 3) disorganized thinking OR altered level of consciousness must be observed in the patient based on information gathered during the 3D-CAM assessment for delirium to be considered present. Should a patient decline participation in the 3D-CAM at a given time point, researchers will still ask that patient to participate at any remaining time point in the study.

All assessments will be performed by individuals rigorously trained in both the full CAM assessment and 3D-CAM assessment.

All procedures in this study will be conducted in the same manner for patients in either the ICU or the PACU. Staff in the PACUs and the ICUs will be informed of the purpose and the procedures of the study.

ii. Sample size

We base our sample size calculations on the unadjusted relationship between PACU delirium and postoperative delirium found in a prior study. This study found the crude odds ratio to be approximately 3.9 (6). Since our first hour after tracheal tube removal delirium measurements and postoperative delirium measurements occur in the same patient, we use the McNemar test for dependent pairs. Conservatively assuming an odds ratio of 3.0, along with 80% power and α of 0.05, two tails, and 30% discordant pairs (6), the required sample size is 100 patients. Assuming 10% of patients are unable to be assessed, we will enroll 110 patients.

iii. Blinding

Researchers responsible for performing delirium assessments in the ICU and PACU as part of this study will be blinded from the patient's group status in the ENGAGES study and will not participate in intraoperative monitoring, postoperative assessments in the first five postoperative days, or delirium chart review. 3D-CAM assessments performed in this study will be reviewed and entered into the REDCap database by a second researcher to ensure accuracy in the delirium assessment.

Assessors of delirium in the postoperative period and in the delirium chart review for the ENGAGES study will be blinded from the results of delirium assessments performed in the ICU and PACU as part of this study.

b. Study group and consenting process

The target population for this study comprises all patients undergoing elective surgery at Barnes Jewish Hospital beginning June 8, 2016 and until the study enrollment goal of 100 assessed patients is reached. Patients who consent to participation in both the SATISFY-SOS and ENGAGES studies are eligible for this study. Patients may choose to refuse participation in this study at any time point.

We note that not all patients undergoing surgical procedures at Barnes Jewish Hospital will have the opportunity to participate in this study.

i. Eligibility criteria

Inclusion criteria:

In order to be included in this study, patients must be:

(i) Enrolled in the SATISFY-SOS study or ENGAGES study (Appendix A);
(ii) Tracheal tube removal on postoperative day 0 before 7pm.

c. Data

The following are the types of data that we anticipate using in this study. These parameters have significant overlap with the data already being collected on patients enrolled in ENGAGES.

We will collect the following patient baseline characteristics: age, sex, race, smoking history, alcohol history, dementia, pre-existing medical or surgical conditions, preoperative medications (including benzodiazepines, antidepressants, neuroleptics, analgesics), previous surgical procedures in the last 3 months. For our analysis, we will be calculating each patient's Charlson Comorbidity Index score and their score on the Short Blessed Test.

We will collect the following data regarding patient surgery: type of surgery, duration of surgery, duration of anesthesia, anesthesia protocol and dose, time of tracheal tube removal, complications or adverse events.

The primary outcome in this study is the presence of delirium During the PACU or ICU stay, delirium assessments using the 3D-CAM will be performed at 30 minutes and at 60 minutes following tracheal tube removal in either the PACU or ICU. If an eligible patient is approached but unable to or declines to participate in the study at either or both time points, the reason(s) for the non-assessment will be recorded. We anticipate reasons for non-assessment to include logistical barrier to approach patient, patient inability to complete the verbal assessment, and active decline to participate by the patient. Patients are considered incapable of verbal communication and completion of delirium assessment at that time if they do not express themselves verbally to any prompt or stimulus. Information regarding the length of stay in PACU or ICU, RASS score at both time points, nurse reports, adverse events, or interventions will also be collected.

Data regarding the postoperative period will also be collected from the ENGAGES database: daily CAM assessments performed according to the ENGAGES protocol, which states that delirium will be diagnosed by a combination of CAM assessments, the full CAM or the CAM-ICU, and the delirium chart review, in which an ENGAGES research team member blinded to the CAM/CAM-ICU results will do a standardized, comprehensive chart review to detect any incidences of delirium and identify postoperative medications, duration of hospital stay, nurse reports, adverse events, or additional interventions. The delirium assessments performed in post-operative days 1-5 as well as the delirium chart review are conducted as part of the ENGAGEs study protocol and provide necessary data for comparison of 3D-CAM assessments performed in the PACU as part of this study. Should this study be emulated at other sites, a delirium assessment method for the postoperative period would also need to be implemented.

All electronic data collected in the course of this study, as well as the SATISFY-SOS and ENGAGES databases, are hosted on a firewall-secured network server. This server is managed and maintained by the IT team of the Department of Anesthesiology, and is securely housed behind two locked doors in the departmental offices. The project Informaticist, Data Manager, and Director(s) are the only individuals with full access to these password-protected and encrypted databases. Delirium assessments performed in the ICU and PACU are completed using paper surveys and are securely stored within the department and their results are entered into a REDCap database.

i. Statistical considerations

First, we will calculate the crude association between delirium within the first hour after tracheal tube removal and postoperative delirium using the McNemar test for two dependent variables.

Multivariable logistic regression will be performed with the presence of delirium in the postoperative period as the dependent variable and the presence of delirium as detected in the PACU or ICU by positive 3D-CAM, which is the principle type of data collected in this study, will serve as the independent variable of interest. We assume a 25% prevalence of postoperative delirium within the first hour following tracheal tube removal in our study population based on previous studies (16,17). With 100 assessed patients, the model would have a sufficient number of outcome events, 25, to include early delirium within the first hour after tracheal tube removal along with three confounders, assuming 6 outcome events are needed per variable (18). The three confounders that will be included in the model are age (continuous), Short Blessed Test (continuous) (19,20), and Charlson Comorbidity Index (continuous) (21,22). Age of 65 years or older, cognitive impairment, dementia, and coexisting medical conditions including multiple comorbidities, chronic renal or hepatic disease, stroke, and neurologic have been consistently described as risk factors for postoperative delirium (23). Though our sample size is relatively small, based on our assumptions there will be sufficient patients to examine the relationship between early-onset delirium and postoperative delirium, factoring in these three confounders. We will perform additional sensitivity analyses using the assumptions that 1) active patient decline of delirium assessment and 2) inability to give verbal responses represent postoperative delirium in the first hour following tracheal tube removal in those patients.

Additional analyses may be performed *post-hoc* with the descriptive data collected through the ENGAGES and SATISFY-SOS databases if they are believed to contain significant confounders, which may include patient comorbidities, adverse events, medications administered, and surgery duration (24).

Coefficients to variables will be considered significant at level of $\alpha<0.05$. Results will be reported as odds ratios with 95% confidence intervals. We pre-specify the minimum important odds ratio for having potential predictive utility would be a >20% change in either direction (i.e. OR < 0.8 or > 1.2) (25). The 3D-CAM is less sensitive than the CAM

for delirium detection (11). Therefore, it is possible that some episodes of delirium in the PACU or ICU will not be detected with the 3D-CAM. This increases the possibility that our study will not detect an association between delirium in the PACU or ICU and postoperative delirium even if such an association is present (i.e., false negative result).

d. Anticipated results

We anticipate that the presence of delirium in the first hour post-tracheal tube removal will be identified as an independent predictor of delirium later on in the postoperative period.

e. Strengths and limitations

i. Strengths

We believe that the 3D-CAM is an appropriate method of assessing for delirium in the PACU or ICU patient population at multiple time points during their stay. Previous studies have suggested that the 3D-CAM has high sensitivity and specificity in detecting delirium, and greater sensitivity when compared to the CAM-ICU (9,11,14).

Performing two brief assessments for delirium at time points 30 and 60 minutes after tracheal tube removal has several advantages. It will allow the assessment of delirium to be more accurate in each patient, increase the likelihood of completing at least one assessment per patient, and track the development of delirium signs over the course of the immediate postoperative period.

ii. Limitations

This study has several limitations. It is being conducted at only one academic medical center, Barnes-Jewish Hospital. The sample is a convenience sample based on surgical patients who have already consented to participation in SATISFY-SOS study and the ENGAGES trial. The sample size of 100 patients is relatively small and will limit the precision of these estimates, but will likely be sufficient for exploration of the primary hypothesis.

We foresee limitations regarding our capacity to accurately monitor tracheal tube removal times, though we will work with PACU and ICU staff in order to communicate effectively and approach patients at our desired time intervals after tracheal tube removal. Researchers will ensure that delirium assessments are performed as close to 30 minutes and 60 minutes post-tracheal tube removal as possible. However, due to logistical considerations such as patient transport and Anesthesia team handoff, patients may not be available to approach for delirium at either time point.

We anticipate that a significant proportion of patients may be unwilling to participate in the 3D-CAM during their stay in the PACU or ICU. For example, many more patients may elect to complete a single 3D-CAM at 30 minutes post-tracheal tube removal rather

than at both time points. Patient responses to the 3D-CAM administered at the 2nd time point may also be influenced by their 3D-CAM at 30 minutes after tracheal tube removal; i.e. they may experience survey fatigue. It is also possible that participation in this study may impact a patient's willingness to continue their enrollment in ENGAGES, including the completion of the full CAM in the first five postoperative days and other types of data collected in ENGAGES.

It is not ideal to compare incidence of emergence delirium as assessed by 3D-CAM in the PACU or ICU with delirium incidence assessed by the unabbreviated CAM, CAM-ICU, or delirium chart review in the postoperative period. While the CAM is a validated instrument for detection of delirium by non-psychiatrists, it does take much longer to administer. As it will be advantageous for this study to assess for delirium at two different time points in a relatively short period, we feel that the advantages of using the 3D-CAM outweigh the possible losses in sensitivity and specificity that will result from departure from the full CAM.

f. Compliance

As this is an observational study, no procedures for monitoring exposure compliance are necessary. Patients may be withdrawn from this study, as well as SATISFY-SOS, or ENGAGES if requested. As described in the consent forms for SATISFY-SOS and ENGAGES, data already collected may continue to be used.

V. Ethical considerations

We have considered the burden imposed on patients having to undergo two successive 3D-CAM assessments in the first hour after tracheal tube removal. As the 3D-CAM is very limited in duration, usually requiring patient participation for 3 minutes (9), we believe the selection of this assessment method is acceptable. We do not believe that participation in the 3D-CAM up to 2 times during PACU or ICU stay will have any negative effects on patient care or postoperative outcomes.

This study has received institutional IRB approval at Washington University School of Medicine IRB ID#201612007 on December 8, 2016.

a. Finance and insurance

This study involves little-to-no risk to patients, and patients will not be compensated for participation. There are no relevant finance details, insurance details, or covers for negligent and non-negligent harm in this study.

b. Reporting and dissemination

Results of this study will be presented at national meetings and published in a scientific journal. Participants will not be individually notified regarding the results of this study.

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VII. Author contributions

VC and CMT contributed equally to study conceptualization, statistical design, protocol drafting, and protocol editing.
VLK contributed to statistical design.
SLM completed the institutional IRB approval process.
MSA contributed to study conceptualization and protocol editing.

VIII. Collaborators

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IX. Funding information

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X. Data Sharing

Data collection for this study is ongoing.

XI. Competing interests

The authors report no conflicts of interest in conducting this study.

Appendix A

a. ENGAGES Inclusion and Exclusion Criteria

Inclusion:

1. Adults older than 60;
2. competent to provide informed consent;
3. undergoing major elective surgery requiring a minimum stay of 2 days postoperatively (e.g., major open cardiac, thoracic, vascular, intra-abdominal, gynecologic, urologic, orthopedic, hepato-biliary and ear, nose and throat surgery);
4. enrolled in the SATISFY-SOS study

Exclusion:

1. Unable to provide informed consent;
2. undergoing neurosurgical procedures;
3. preoperative delirium;
4. unable to participate adequately in delirium screening including those who are blind, deaf, illiterate or not fluent in English;
5. history of intraoperative awareness;
6. additional surgery planned within five days of index surgery

b. SATISFY-SOS Inclusion and Exclusion Criteria

Inclusion:

1. Surgical and procedural patients who require anesthesia services

Exclusion:

1. Patients under the age of 18 years

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***
Title: **Protocol for an observational study of delirium in the Post-Anesthesia Care Unit (PACU) as a potential predictor of subsequent postoperative delirium**

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract **Complete (Page 1)**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **Complete (Page 4)**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **Complete (Pages 5-8)**
Objectives	3	State specific objectives, including any prespecified hypotheses **Complete (Page 7)**
Methods		
Study design	4	Present key elements of study design early in the paper **Complete (Pages 8-12)**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **Complete (Pages 8-12)**
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants **Complete (Page 9)**
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **Complete (Pages 10-12)**
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 **Complete (Pages 10-12)**
Bias	9	Describe any efforts to address potential sources of bias **Complete (Page 9, 11)**
Study size	10	Explain how the study size was arrived at **Complete (Page 11-12)**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **Complete (Pages 10-12)**
Statistical methods	12	**Complete (Pages 10-12)**
		(*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*) If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses
Results		
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 **Complete (Pages 8-11)**

		(b) Give reasons for non-participation at each stage **Complete (Pages 8-11)**
		(c) Consider use of a flow diagram **Complete (Pages 8-11)**
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **Complete (Pages 8-13)**
		(b) Indicate number of participants with missing data for each variable of interest **Data collection ongoing**
Outcome data	15*	Report numbers of outcome events or summary measures **Data collection ongoing**
Main results	16	**Data collection ongoing**
		(*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
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **Data collection ongoing**
Discussion		**Data collection ongoing**
Key results	18	Summarise key results with reference to study objectives
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
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
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 **Complete (Page 16)**

*Give information separately for exposed and unexposed groups.

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.