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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

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Table of Contents

- I. Abstract
- II. Article summary
 - a. Strengths and limitations
- III. Introduction
 - a. Background and rationale
 - b. Specific aims
 - c. Significance
- IV. Methods and analysis
 - a. Study Design
 - i. Delirium assessment method
 - ii. Sample size
 - iii. Blinding
 - b. Study group and consenting process
 - i. Eligibility criteria
 - c. Data
 - i. Statistical considerations
 - d. Anticipated results
 - e. Strengths and Limitations
 - i. Strengths
 - ii. Limitations
 - f. Compliance
- V. Ethical considerations
 - a. Finance and insurance
 - b. Reporting and dissemination
- VI. References
- VII. Author contributions
- VIII. Collaborators
- IX. Funding information
- X. Data Sharing
- XI. Competing interests
- XII. Appendix A

1
2
3
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For peer review only

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

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3 of general anesthesia, and should theoretically resolve within minutes to hours.
4 Postoperative delirium, arbitrarily defined as occurring 1 to 5 days following surgery,
5 may have distinct etiologies from emergence delirium in the PACU. The relationship
6 between delirium occurring immediately following surgery and emergence from
7 anesthesia and postoperative delirium after the day of surgery is currently not known.
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11 Several studies have suggested an association between emergence delirium,
12 manifesting in the PACU, and postoperative delirium, manifesting after the day of
13 surgery (6–9). However, these studies each employed different methods for assessing
14 emergence delirium. Card et al. used the Confusion Assessment Method for the
15 Intensive Care Unit (CAM-ICU) for identifying patients with delirium, and the Richmond
16 Agitation-Sedation Scale (RASS) to classify the delirium as hyper or hypoactive (6,10–
17 12). This study found that of the 16% of subjects found to have delirium signs during
18 their PACU stay, when assessed at 30min, 60min, and at discharge, 92% exhibited
19 signs of the hypoactive subtype and 8% exhibited signs of the hyperactive subtype (6).
20 This is compared to the findings at time of PACU admission when 31% of patients had
21 signs of delirium of which, 56% exhibited signs of the hypoactive subtype and 44%
22 exhibited signs of the hyperactive subtype (6). A study of 91 patients conducted by
23 Neufeld et al. using psychiatrist evaluation based on DSM4 criteria found a 45%
24 prevalence of delirium in the PACU (8). Out of 19 episodes of postoperative delirium
25 found, 14 (74%) had experienced emergence delirium while in the PACU (8). Using the
26 Nu-DESC assessment for delirium, a cumulative observational scoring system including
27 disorientation, inappropriate behavior, inappropriate communication,
28 illusions/hallucinations, and psychomotor retardation, assessed in three time periods for
29 a total of 12 hours, Radtke et al. observed an 11% prevalence of emergence delirium in
30 the PACU (7). Of 38 patients who experienced delirium in the first postoperative day
31 (38/862 = 4.2%), 32 (84.2%) had previously displayed emergence delirium (7). In their
32 population of 47 hip-fracture repair patients, Sharma et al. employed the unabbreviated
33 Confusion Assessment Method (CAM) assessment at 60 minutes after discontinuation
34 of isoflurane and found a prevalence of emergence delirium of 45%. Of these patients,
35 36% subsequently experienced postoperative delirium, and delirium in the PACU was a
36 strong predictor of subsequent postoperative delirium, according to a Fisher's Exact
37 Test ($P < 0.001$) with 100% sensitivity and 85% specificity. (9).
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44 The Confusion Assessment Method (CAM) is a validated and widely-used delirium
45 assessment instrument that is used primarily by non-psychiatrists (13). Both the CAM-
46 ICU and the 3-minute Diagnostic Confusion Assessment Method (3D-CAM) are
47 abbreviated delirium assessments derived from the CAM, with the CAM-ICU designed
48 specifically for assessing intubated or nonverbal patients (11,12). The 3D-CAM consists
49 of a subset of the assessment components used in the CAM, designed to only take 3
50 minutes, supplemented by a series of questions regarding patient behavior during the
51 interview to be completed by the interviewer following the patient visit (11). The major
52 advantage of both the 3D-CAM and CAM-ICU compared to the unabbreviated CAM are
53 the assessments' relative brevity.
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3 The 3D-CAM and CAM-ICU require similar time to complete. A previous study
4 comparing related methods of delirium assessment estimated sensitivity of 93% and
5 specificity of 96% for the 3D-CAM in detecting delirium in patients without dementia as
6 compared to the CAM (11). A study comparing the 3D-CAM and CAM-ICU directly in a
7 general medicine patient population aged >75 found a 95% sensitivity for the 3D CAM
8 [95% CI 74-100%] and a 53% sensitivity for the CAM-ICU [95% CI 29-76%] (14). The
9 3D-CAM and CAM-ICU were both reported as having >90% specificity for detecting
10 delirium (14). Unlike the CAM-ICU, the 3D-CAM requires the patient to verbally answer
11 questions assessing for orientation and attention. These features are emphasized in the
12 DSM-V over altered level of consciousness, which the CAM-ICU assesses by
13 incorporating the RASS score into its delirium assessment (11). In this study, the 3D-
14 CAM is chosen over the CAM-ICU its higher sensitivity in detecting delirium in verbal
15 patients.
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20 b. Specific aims

21 Aim 1

22 This study aims to determine if delirium in the first hour post-tracheal tube removal is
23 predictive of delirium in the five subsequent postoperative days.
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27 We hypothesize that delirium in the first hour post-tracheal tube removal is
28 independently predictive of delirium manifesting during postoperative days 1-5.
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31 c. Significance

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

41 a. Study design

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43 This retrospective study is a sub-study of both the Electroencephalography Guidance of
44 Anesthesia to Alleviate Geriatric Syndromes Study (ENGAGES, NCT02241655) and the
45 Systematic Assessment and Targeted Improvement of Services Following Yearlong
46 Surgical Outcomes Surveys Study (SATISFY-SOS, NCT02032030), being conducted at
47 Washington University. ENGAGES is a randomized clinical trial to determine whether
48 EEG-guided anesthesia care can reduce the incidence of postoperative delirium and
49 improve health-related quality of life postoperatively, when compared to usual
50 anesthesia care. SATISFY-SOS is an ongoing cohort study that is obtaining detailed
51 information on unselected surgical patients, and is tracking their health and well-being in
52 the intermediate term postoperatively. All members of the ENGAGES trial are also
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3 enrolled in SATISFY-SOS, and the patients included in the current study will be
4 comprised of ENGAGES participants only.
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7 i. Delirium assessment method
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10 The primary outcome in this study is the presence of delirium in the immediate
11 postoperative period, within 1 hour following tracheal tube removal after the completion
12 of surgery.
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14 Only patients who are not delirious prior to surgery are enrolled in the ENGAGES trial.
15 As stated in the SATISFY-SOS consent, patients can be assessed for delirium up to two
16 times per day. In this sub-study, 3D-CAM assessments will be performed in the PACU
17 or ICU at 30 minutes and at 1 hour following tracheal tube removal. The presence of
18 delirium in the first hour will be defined as a positive 3D-CAM assessment at either of
19 these two time points. The characteristics of 1) acute onset/fluctuating course, 2)
20 inattention, and 3) disorganized thinking OR altered level of consciousness must be
21 observed in the patient based on information gathered during the 3D-CAM assessment
22 for delirium to be considered present. Should a patient decline participation in the 3D-
23 CAM at a given time point, researchers will still ask that patient to participate at any
24 remaining time point in the study.
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28 All assessments will be performed by individuals rigorously trained in both the full CAM
29 assessment and 3D-CAM assessment.
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32 All procedures in this study will be conducted in the same manner for patients in either
33 the ICU or the PACU. Staff in the PACUs and the ICUs will be informed of the purpose
34 and the procedures of the study.
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37 ii. Sample size
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39 We base our sample size calculations on the unadjusted relationship between PACU
40 delirium and postoperative delirium found in a prior study. This study found the crude
41 odds ratio to be approximately 3.9 (6). Since our first hour after tracheal tube removal
42 delirium measurements and postoperative delirium measurements occur in the same
43 patient, we use the McNemar test for dependent pairs. Conservatively assuming an
44 odds ratio of 3.0, along with 80% power and α of 0.05, two tails, and 30% discordant
45 pairs (6), the required sample size is 100 patients. Assuming 10% of patients are unable
46 to be assessed, we will enroll 110 patients.
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50 iii. Blinding
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53 Researchers responsible for performing delirium assessments in the ICU and PACU as
54 part of this study will be blinded from the patient's group status in the ENGAGES study
55 and will not participate in intraoperative monitoring, postoperative assessments in the
56 first five postoperative days, or delirium chart review. 3D-CAM assessments performed
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3 in this study will be reviewed and entered into the REDCap database by a second
4 researcher to ensure accuracy in the delirium assessment.
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7 Assessors of delirium in the postoperative period and in the delirium chart review for the
8 ENGAGES study will be blinded from the results of delirium assessments performed in
9 the ICU and PACU as part of this study.
10

11 b. Study group and consenting process

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13
14 The target population for this study comprises all patients undergoing elective surgery at
15 Barnes Jewish Hospital beginning June 8, 2016 and until the study enrollment goal of
16 100 assessed patients is reached. Patients who consent to participation in both the
17 SATISFY-SOS and ENGAGES studies are eligible for this study. Patients may choose
18 to refuse participation in this study at any time point.
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21 We note that not all patients undergoing surgical procedures at Barnes Jewish Hospital
22 will have the opportunity to participate in this study.
23

24 i. Eligibility criteria

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27 Inclusion criteria:

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

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31
32 (i) Enrolled in the SATISFY-SOS study or ENGAGES study (Appendix A);
33 (ii) Tracheal tube removal on postoperative day 0 before 7pm.
34

35 c. Data

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38 The following are the types of data that we anticipate using in this study. These
39 parameters have significant overlap with the data already being collected on patients
40 enrolled in ENGAGES.
41

42 We will collect the following patient baseline characteristics: age, sex, race, smoking
43 history, alcohol history, dementia, pre-existing medical or surgical conditions,
44 preoperative medications (including benzodiazepines, antidepressants, neuroleptics,
45 analgesics), previous surgical procedures in the last 3 months. For our analysis, we will
46 be calculating each patient's Charlson Comorbidity Index score and their score on the
47 Short Blessed Test.
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49

50 We will collect the following data regarding patient surgery: type of surgery, duration of
51 surgery, duration of anesthesia, anesthesia protocol and dose, time of tracheal tube
52 removal, complications or adverse events.
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55 The primary outcome in this study is the presence of delirium During the PACU or ICU
56 stay, delirium assessments using the 3D-CAM will be performed at 30 minutes and at
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3 60 minutes following tracheal tube removal in either the PACU or ICU. If an eligible
4 patient is approached but unable to or declines to participate in the study at either or
5 both time points, the reason(s) for the non-assessment will be recorded. We anticipate
6 reasons for non-assessment to include logistical barrier to approach patient, patient
7 inability to complete the verbal assessment, and active decline to participate by the
8 patient. Patients are considered incapable of verbal communication and completion of
9 delirium assessment at that time if they do not express themselves verbally to any
10 prompt or stimulus. Information regarding the length of stay in PACU or ICU, RASS
11 score at both time points, nurse reports, adverse events, or interventions will also be
12 collected.
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16 Data regarding the postoperative period will also be collected from the ENGAGES
17 database: daily CAM assessments performed according to the ENGAGES protocol,
18 which states that delirium will be diagnosed by a combination of CAM assessments, the
19 full CAM or the CAM-ICU, and the delirium chart review, where a researcher blinded to
20 the CAM/CAM-ICU results will do a comprehensive chart review to detect any
21 incidences of delirium and identify postoperative medications, duration of hospital stay,
22 nurse reports, adverse events, or additional interventions.
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25
26 All electronic data collected in the course of this study, as well as the SATISFY-SOS
27 and ENGAGES databases, are hosted on a firewall-secured network server. This server
28 is managed and maintained by the IT team of the Department of Anesthesiology, and is
29 securely housed behind two locked doors in the departmental offices. The project
30 Informaticist, Data Manager, and Director(s) are the only individuals with full access to
31 these password-protected and encrypted databases. Delirium assessments performed
32 in the ICU and PACU are completed using paper surveys and are securely stored within
33 the department and their results are entered into a REDCap database.
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36 37 i. Statistical considerations

38
39 First, we will calculate the crude association between delirium within the first hour after
40 tracheal tube removal and postoperative delirium using the McNemar test for two
41 dependent variables.
42
43

44 Multivariable logistic regression will be performed with the presence of delirium in the
45 postoperative period as the dependent variable and the presence of delirium as
46 detected in the PACU or ICU by positive 3D-CAM, which is the principle type of data
47 collected in this study, will serve as the independent variable of interest. We assume a
48 25% prevalence of postoperative delirium within the first hour following tracheal tube
49 removal in our study population based on previous studies (15,16). With 100 assessed
50 patients, the model would have a sufficient number of outcome events (25) to include
51 early delirium within the first hour after tracheal tube removal along with three
52 confounders, assuming 6 outcome events are needed per variable (17). The three
53 confounders that will be included in the model are age (continuous), Short Blessed Test
54 (continuous) (18,19), and Charlson Comorbidity Index (continuous) (20,21). Age of 65
55 years or older, cognitive impairment, dementia, and coexisting medical conditions
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3 including multiple comorbidities, chronic renal or hepatic disease, stroke, and neurologic
4 have been consistently described as risk factors for postoperative delirium (22). We will
5 perform additional sensitivity analyses using the assumptions that 1) active patient
6 decline of delirium assessment and 2) inability to give verbal responses represent
7 postoperative delirium in the first hour following tracheal tube removal in those patients.
8
9

10 Additional analyses may be performed *post-hoc* with the descriptive data collected
11 through the ENGAGES and SATISFY-SOS databases if they are believed to contain
12 significant confounders.
13

14
15 Coefficients to variables will be considered significant at level of $\alpha < 0.05$. Results will be
16 reported as odds ratios with 95% confidence intervals. We pre-specify the minimum
17 important odds ratio for having potential predictive utility would be a >20% change in
18 either direction (i.e. OR < 0.8 or > 1.2) (23). The 3D-CAM is less sensitive than the CAM
19 for delirium detection (11). Therefore, it is possible that some episodes of delirium in the
20 PACU or ICU will not be detected with the 3D-CAM. This increases the possibility that
21 our study will not detect an association between delirium in the PACU or ICU and
22 postoperative delirium even if such an association is present (i.e., false negative result).
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26 d. Anticipated results

27
28 We anticipate that the presence of delirium in the first hour post-tracheal tube removal
29 will be identified as an independent predictor of delirium later on in the postoperative
30 period.
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33 e. Strengths and limitations

34 i. Strengths

35
36 We believe that the 3D-CAM is an appropriate method of assessing for delirium in the
37 PACU or ICU patient population at multiple time points during their stay. Previous
38 studies have suggested that the 3D-CAM has high sensitivity and specificity in detecting
39 delirium, and greater sensitivity when compared to the CAM-ICU (9,11,14).
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43
44 Performing two brief assessments for delirium at time points 30 and 60 minutes after
45 tracheal tube removal has several advantages. It will allow the assessment of delirium
46 to be more accurate in each patient, increase the likelihood of completing at least one
47 assessment per patient, and track the development of delirium signs over the course of
48 the immediate postoperative period.
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51 ii. Limitations

52
53 This study has several limitations. It is being conducted at only one academic medical
54 center, Barnes-Jewish Hospital. The sample is a convenience sample based on surgical
55 patients who have already consented to participation in SATISFY-SOS study and the
56 ENGAGES trial.
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5 We foresee limitations regarding our capacity to accurately monitor tracheal tube
6 removal times, though we will work with PACU and ICU staff in order to communicate
7 effectively and approach patients at our desired time intervals after tracheal tube
8 removal. Researchers will ensure that delirium assessments are performed as close to
9 30 minutes and 60 minutes post-tracheal tube removal as possible. However, due to
10 logistical considerations such as patient transport and Anesthesia team handoff,
11 patients may not be available to approach for delirium at either time point.
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13
14 We anticipate that a significant proportion of patients may be unwilling to participate in
15 the 3D-CAM during their stay in the PACU or ICU. For example, many more patients
16 may elect to complete a single 3D-CAM at 30 minutes post-tracheal tube removal rather
17 than at both time points. Patient responses to the 3D-CAM administered at the 2nd time
18 point may also be influenced by their 3D-CAM at 30 minutes after tracheal tube
19 removal; i.e. they may experience survey fatigue. It is also possible that participation in
20 this study may impact a patient's willingness to continue their enrollment in ENGAGES,
21 including the completion of the full CAM in the first five postoperative days and other
22 types of data collected in ENGAGES.
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25
26 It is not ideal to compare incidence of emergence delirium as assessed by 3D-CAM in
27 the PACU or ICU with delirium incidence assessed by the unabbreviated CAM, CAM-
28 ICU, or delirium chart review in the postoperative period. While the CAM is a validated
29 instrument for detection of delirium by non-psychiatrists, it does take much longer to
30 administer. As it will be advantageous for this study to assess for delirium at two
31 different time points in a relatively short period, we feel that the advantages of using the
32 3D-CAM outweigh the possible losses in sensitivity and specificity that will result from
33 departure from the full CAM.
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36 f. Compliance

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39 As this is an observational study, no procedures for monitoring exposure compliance
40 are necessary. Patients may be withdrawn from this study, as well as SATISFY-SOS, or
41 ENGAGES if requested. As described in the consent forms for SATISFY-SOS and
42 ENGAGES, data already collected may continue to be used.
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44

45 V. Ethical considerations

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47
48 We have considered the burden imposed on patients having to undergo two successive
49 3D-CAM assessments in the first hour after tracheal tube removal. As the 3D-CAM is
50 very limited in duration, usually requiring patient participation for 3 minutes (9), we
51 believe the selection of this assessment method is acceptable. We do not believe that
52 participation in the 3D-CAM up to 2 times during PACU or ICU stay will have any
53 negative effects on patient care or postoperative outcomes.
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56 This study has received institutional IRB approval at Washington University School of
57 Medicine IRB ID#201612007 on December 8, 2016.
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5 a. Finance and insurance
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7 This study involves little-to-no risk to patients, and patients will not be compensated for
8 participation. There are no relevant finance details, insurance details, or covers for
9 negligent and non-negligent harm in this study.
10

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12 b. Reporting and dissemination
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14 Results of this study will be presented at national meetings and published in a scientific
15 journal. Participants will not be individually notified regarding the results of this study.
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17
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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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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:

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1. Surgical and procedural patients who require anesthesia services

Exclusion:

1. Patients under the age of 18 years

For peer review only

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.

BMJ Open

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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Manuscripts

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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Table of Contents

- I. Abstract
- II. Article summary
 - a. Strengths and limitations
- III. Introduction
 - a. Background and rationale
 - b. Specific aims
 - c. Significance
- IV. Methods and analysis
 - a. Study Design
 - i. Delirium assessment method
 - ii. Sample size
 - iii. Blinding
 - b. Study group and consenting process
 - i. Eligibility criteria
 - c. Data
 - i. Statistical considerations
 - d. Anticipated results
 - e. Strengths and Limitations
 - i. Strengths
 - ii. Limitations
 - f. Compliance
- V. Ethical considerations
 - a. Finance and insurance
 - b. Reporting and dissemination
- VI. References
- VII. Author contributions
- VIII. Collaborators
- IX. Funding information
- X. Data Sharing
- XI. Competing interests

Appendix A – See separate file

1
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For peer review only

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

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3 of general anesthesia, and should theoretically resolve within minutes to hours.
4 Postoperative delirium, arbitrarily defined as occurring 1 to 5 days following surgery,
5 may have distinct etiologies from emergence delirium in the PACU. The relationship
6 between delirium occurring immediately following surgery and emergence from
7 anesthesia and postoperative delirium after the day of surgery is currently not known.
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11 Several studies have suggested an association between emergence delirium,
12 manifesting in the PACU, and postoperative delirium, manifesting after the day of
13 surgery (6–9). However, these studies each employed different methods for assessing
14 emergence delirium. Card et al. used the Confusion Assessment Method for the
15 Intensive Care Unit (CAM-ICU) for identifying patients with delirium, and the Richmond
16 Agitation-Sedation Scale (RASS) to classify the delirium as hyper or hypoactive (6,10–
17 12). This study found that of the 16% of subjects found to have delirium signs during
18 their PACU stay, when assessed at 30min, 60min, and at discharge, 92% exhibited
19 signs of the hypoactive subtype and 8% exhibited signs of the hyperactive subtype (6).
20 This is compared to the findings at time of PACU admission when 31% of patients had
21 signs of delirium of which, 56% exhibited signs of the hypoactive subtype and 44%
22 exhibited signs of the hyperactive subtype (6). A study of 91 patients conducted by
23 Neufeld et al. using psychiatrist evaluation based on DSM4 criteria found a 45%
24 prevalence of delirium in the PACU (8). Out of 19 episodes of postoperative delirium
25 found, 14 (74%) had experienced emergence delirium while in the PACU (8). Using the
26 Nu-DESC assessment for delirium, a cumulative observational scoring system including
27 disorientation, inappropriate behavior, inappropriate communication,
28 illusions/hallucinations, and psychomotor retardation, assessed in three time periods for
29 a total of 12 hours, Radtke et al. observed an 11% prevalence of emergence delirium in
30 the PACU (7). Of 38 patients who experienced delirium in the first postoperative day
31 (38/862 = 4.2%), 32 (84.2%) had previously displayed emergence delirium (7). In their
32 population of 47 hip-fracture repair patients, Sharma et al. employed the unabbreviated
33 Confusion Assessment Method (CAM) assessment at 60 minutes after discontinuation
34 of isoflurane and found a prevalence of emergence delirium of 45%. Of these patients,
35 36% subsequently experienced postoperative delirium, and delirium in the PACU was a
36 strong predictor of subsequent postoperative delirium, according to a Fisher's Exact
37 Test ($P < 0.001$) with 100% sensitivity and 85% specificity. (9).
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44 The Confusion Assessment Method (CAM) is a validated and widely-used delirium
45 assessment instrument that is used primarily by non-psychiatrists (13). Both the CAM-
46 ICU and the 3-minute Diagnostic Confusion Assessment Method (3D-CAM) are
47 abbreviated delirium assessments derived from the CAM, with the CAM-ICU designed
48 specifically for assessing intubated or nonverbal patients (11,12). The 3D-CAM consists
49 of a subset of the assessment components used in the CAM, designed to only take 3
50 minutes, supplemented by a series of questions regarding patient behavior during the
51 interview to be completed by the interviewer following the patient visit (11). The major
52 advantage of both the 3D-CAM and CAM-ICU compared to the unabbreviated CAM are
53 the assessments' relative brevity.
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3 The 3D-CAM and CAM-ICU require similar time to complete. A previous study
4 comparing related methods of delirium assessment estimated sensitivity of 93% and
5 specificity of 96% for the 3D-CAM in detecting delirium in patients without dementia as
6 compared to the CAM (11). A study comparing the 3D-CAM and CAM-ICU directly in a
7 general medicine patient population aged >75 found a 95% sensitivity for the 3D CAM
8 [95% CI 74-100%] and a 53% sensitivity for the CAM-ICU [95% CI 29-76%] (14). The
9 3D-CAM and CAM-ICU were both reported as having >90% specificity for detecting
10 delirium (14). Unlike the CAM-ICU, the 3D-CAM requires the patient to verbally answer
11 questions assessing for orientation and attention. These features are emphasized in the
12 DSM-V over altered level of consciousness, which the CAM-ICU assesses by
13 incorporating the RASS score into its delirium assessment (11). In this study, the 3D-
14 CAM is chosen over the CAM-ICU its higher sensitivity in detecting delirium in verbal
15 patients.
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20 A strong association between emergence delirium as occurring in the PACU and
21 delirium in the post-operative period would suggest the need for changes or additions to
22 the standard of care for patients in the PACU. These changes could include delirium
23 prevention methods, reliable identification of patients presenting with delirium, and
24 prompt treatment of delirium.
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27 Several interventions have been previously shown to reduce the rates of delirium
28 developing during hospital care: regular orienting of patients to time and surroundings,
29 reducing visual and auditory sensory deficits, maintaining adequate nutrition and fluids,
30 ensuring adequate environment for sleep, encouraging mobility, and reducing use of
31 medical restraints (2). Identification of delirium can be facilitated with the use of
32 validated bedside screening methods such as the 3D-CAM or CAM-ICU by non-
33 psychiatrist healthcare personnel. Non-pharmacological measures such as
34 reorientation, correction of sensory deficits, providing a calm patient-care setting with
35 fewer disturbances, and encouraging adequate sleep are preferred over the use of
36 medications to treat acute delirium (2)
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40 Signs of delirium such as fluctuating level of consciousness and disorganized thinking
41 should not be considered as part of the “normal” course for patients in the PACU.
42 Instead, healthcare teams should integrate these findings into their care of patients and
43 in recommendations given with patient hand-off following PACU stay. These findings
44 should be considered when addressing each patient’s pain, analgesia regimen,
45 sedation, and target sedation score as part of a tailored delirium treatment regimen(15).
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48 b. Specific aims 49

50 Aim 1

51 This study aims to determine if delirium in the first hour post-tracheal tube removal is
52 predictive of delirium in the five subsequent postoperative days.
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55 We hypothesize that delirium in the first hour post-tracheal tube removal is
56 independently predictive of delirium manifesting during postoperative days 1-5.
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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.

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4 All procedures in this study will be conducted in the same manner for patients in either
5 the ICU or the PACU. Staff in the PACUs and the ICUs will be informed of the purpose
6 and the procedures of the study.
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10 ii. Sample size

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

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25 Researchers responsible for performing delirium assessments in the ICU and PACU as
26 part of this study will be blinded from the patient's group status in the ENGAGES study
27 and will not participate in intraoperative monitoring, postoperative assessments in the
28 first five postoperative days, or delirium chart review. 3D-CAM assessments performed
29 in this study will be reviewed and entered into the REDCap database by a second
30 researcher to ensure accuracy in the delirium assessment.
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33 Assessors of delirium in the postoperative period and in the delirium chart review for the
34 ENGAGES study will be blinded from the results of delirium assessments performed in
35 the ICU and PACU as part of this study.
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38 b. Study group and consenting process

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40 The target population for this study comprises all patients undergoing elective surgery at
41 Barnes Jewish Hospital beginning June 8, 2016 and until the study enrollment goal of
42 100 assessed patients is reached. Patients who consent to participation in both the
43 SATISFY-SOS and ENGAGES studies are eligible for this study. Patients may choose
44 to refuse participation in this study at any time point.
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47 We note that not all patients undergoing surgical procedures at Barnes Jewish Hospital
48 will have the opportunity to participate in this study.
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51 i. Eligibility criteria

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53 Inclusion criteria:

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55 In order to be included in this study, patients must be:
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3 (i) Enrolled in the SATISFY-SOS study or ENGAGES study (Appendix A);
4 (ii) Tracheal tube removal on postoperative day 0 before 7pm.
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7 c. Data
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9 The following are the types of data that we anticipate using in this study. These
10 parameters have significant overlap with the data already being collected on patients
11 enrolled in ENGAGES.
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13 We will collect the following patient baseline characteristics: age, sex, race, smoking
14 history, alcohol history, dementia, pre-existing medical or surgical conditions,
15 preoperative medications (including benzodiazepines, antidepressants, neuroleptics,
16 analgesics), previous surgical procedures in the last 3 months. For our analysis, we will
17 be calculating each patient's Charlson Comorbidity Index score and their score on the
18 Short Blessed Test.
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21 We will collect the following data regarding patient surgery: type of surgery, duration of
22 surgery, duration of anesthesia, anesthesia protocol and dose, time of tracheal tube
23 removal, complications or adverse events.
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27 The primary outcome in this study is the presence of delirium During the PACU or ICU
28 stay, delirium assessments using the 3D-CAM will be performed at 30 minutes and at
29 60 minutes following tracheal tube removal in either the PACU or ICU. If an eligible
30 patient is approached but unable to or declines to participate in the study at either or
31 both time points, the reason(s) for the non-assessment will be recorded. We anticipate
32 reasons for non-assessment to include logistical barrier to approach patient, patient
33 inability to complete the verbal assessment, and active decline to participate by the
34 patient. Patients are considered incapable of verbal communication and completion of
35 delirium assessment at that time if they do not express themselves verbally to any
36 prompt or stimulus. Information regarding the length of stay in PACU or ICU, RASS
37 score at both time points, nurse reports, adverse events, or interventions will also be
38 collected.
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42 Data regarding the postoperative period will also be collected from the ENGAGES
43 database: daily CAM assessments performed according to the ENGAGES protocol,
44 which states that delirium will be diagnosed by a combination of CAM assessments, the
45 full CAM or the CAM-ICU, and the delirium chart review, in which an ENGAGES
46 research team member blinded to the CAM/CAM-ICU results will do a standardized,
47 comprehensive chart review to detect any incidences of delirium and identify
48 postoperative medications, duration of hospital stay, nurse reports, adverse events, or
49 additional interventions. The delirium assessments performed in post-operative days 1-
50 5 as well as the delirium chart review are conducted as part of the ENGAGES study
51 protocol and provide necessary data for comparison of 3D-CAM assessments
52 performed in the PACU as part of this study. Should this study be emulated at other
53 sites, a delirium assessment method for the postoperative period would also need to be
54 implemented.
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5 All electronic data collected in the course of this study, as well as the SATISFY-SOS
6 and ENGAGES databases, are hosted on a firewall-secured network server. This server
7 is managed and maintained by the IT team of the Department of Anesthesiology, and is
8 securely housed behind two locked doors in the departmental offices. The project
9 Informaticist, Data Manager, and Director(s) are the only individuals with full access to
10 these password-protected and encrypted databases. Delirium assessments performed
11 in the ICU and PACU are completed using paper surveys and are securely stored within
12 the department and their results are entered into a REDCap database.
13

14 15 i. Statistical considerations 16

17
18 First, we will calculate the crude association between delirium within the first hour after
19 tracheal tube removal and postoperative delirium using the McNemar test for two
20 dependent variables.
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22
23 Multivariable logistic regression will be performed with the presence of delirium in the
24 postoperative period as the dependent variable and the presence of delirium as
25 detected in the PACU or ICU by positive 3D-CAM, which is the principle type of data
26 collected in this study, will serve as the independent variable of interest. We assume a
27 25% prevalence of postoperative delirium within the first hour following tracheal tube
28 removal in our study population based on previous studies (16,17). With 100 assessed
29 patients, the model would have a sufficient number of outcome events, 25, to include
30 early delirium within the first hour after tracheal tube removal along with three
31 confounders, assuming 6 outcome events are needed per variable (18). The three
32 confounders that will be included in the model are age (continuous), Short Blessed Test
33 (continuous) (19,20), and Charlson Comorbidity Index (continuous) (21,22). Age of 65
34 years or older, cognitive impairment, dementia, and coexisting medical conditions
35 including multiple comorbidities, chronic renal or hepatic disease, stroke, and neurologic
36 have been consistently described as risk factors for postoperative delirium (23). Though
37 our sample size is relatively small, based on our assumptions there will be sufficient
38 patients to examine the relationship between early-onset delirium and postoperative
39 delirium, factoring in these three confounders. We will perform additional sensitivity
40 analyses using the assumptions that 1) active patient decline of delirium assessment
41 and 2) inability to give verbal responses represent postoperative delirium in the first
42 hour following tracheal tube removal in those patients.
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48 Additional analyses may be performed *post-hoc* with the descriptive data collected
49 through the ENGAGES and SATISFY-SOS databases if they are believed to contain
50 significant confounders, which may include patient comorbidities, adverse events,
51 medications administered, and surgery duration (24).
52

53
54 Coefficients to variables will be considered significant at level of $\alpha < 0.05$. Results will be
55 reported as odds ratios with 95% confidence intervals. We pre-specify the minimum
56 important odds ratio for having potential predictive utility would be a >20% change in
57 either direction (i.e. OR < 0.8 or > 1.2) (25). The 3D-CAM is less sensitive than the CAM
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3 for delirium detection (11). Therefore, it is possible that some episodes of delirium in the
4 PACU or ICU will not be detected with the 3D-CAM. This increases the possibility that
5 our study will not detect an association between delirium in the PACU or ICU and
6 postoperative delirium even if such an association is present (i.e., false negative result).
7
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9
10 d. Anticipated results

11 We anticipate that the presence of delirium in the first hour post-tracheal tube removal
12 will be identified as an independent predictor of delirium later on in the postoperative
13 period.
14

15
16 e. Strengths and limitations

17
18 i. Strengths

19
20 We believe that the 3D-CAM is an appropriate method of assessing for delirium in the
21 PACU or ICU patient population at multiple time points during their stay. Previous
22 studies have suggested that the 3D-CAM has high sensitivity and specificity in detecting
23 delirium, and greater sensitivity when compared to the CAM-ICU (9,11,14).
24
25

26
27 Performing two brief assessments for delirium at time points 30 and 60 minutes after
28 tracheal tube removal has several advantages. It will allow the assessment of delirium
29 to be more accurate in each patient, increase the likelihood of completing at least one
30 assessment per patient, and track the development of delirium signs over the course of
31 the immediate postoperative period.
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34
35 ii. Limitations

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37 This study has several limitations. It is being conducted at only one academic medical
38 center, Barnes-Jewish Hospital. The sample is a convenience sample based on surgical
39 patients who have already consented to participation in SATISFY-SOS study and the
40 ENGAGES trial. The sample size of 100 patients is relatively small and will limit the
41 precision of these estimates, but will likely be sufficient for exploration of the primary
42 hypothesis.
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46 We foresee limitations regarding our capacity to accurately monitor tracheal tube
47 removal times, though we will work with PACU and ICU staff in order to communicate
48 effectively and approach patients at our desired time intervals after tracheal tube
49 removal. Researchers will ensure that delirium assessments are performed as close to
50 30 minutes and 60 minutes post-tracheal tube removal as possible. However, due to
51 logistical considerations such as patient transport and Anesthesia team handoff,
52 patients may not be available to approach for delirium at either time point.
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55
56 We anticipate that a significant proportion of patients may be unwilling to participate in
57 the 3D-CAM during their stay in the PACU or ICU. For example, many more patients
58 may elect to complete a single 3D-CAM at 30 minutes post-tracheal tube removal rather
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3 than at both time points. Patient responses to the 3D-CAM administered at the 2nd time
4 point may also be influenced by their 3D-CAM at 30 minutes after tracheal tube
5 removal; i.e. they may experience survey fatigue. It is also possible that participation in
6 this study may impact a patient's willingness to continue their enrollment in ENGAGES,
7 including the completion of the full CAM in the first five postoperative days and other
8 types of data collected in ENGAGES.
9
10

11
12 It is not ideal to compare incidence of emergence delirium as assessed by 3D-CAM in
13 the PACU or ICU with delirium incidence assessed by the unabbreviated CAM, CAM-
14 ICU, or delirium chart review in the postoperative period. While the CAM is a validated
15 instrument for detection of delirium by non-psychiatrists, it does take much longer to
16 administer. As it will be advantageous for this study to assess for delirium at two
17 different time points in a relatively short period, we feel that the advantages of using the
18 3D-CAM outweigh the possible losses in sensitivity and specificity that will result from
19 departure from the full CAM.
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21

22 f. Compliance 23 24

25 As this is an observational study, no procedures for monitoring exposure compliance
26 are necessary. Patients may be withdrawn from this study, as well as SATISFY-SOS, or
27 ENGAGES if requested. As described in the consent forms for SATISFY-SOS and
28 ENGAGES, data already collected may continue to be used.
29
30

31 V. Ethical considerations 32 33

34 We have considered the burden imposed on patients having to undergo two successive
35 3D-CAM assessments in the first hour after tracheal tube removal. As the 3D-CAM is
36 very limited in duration, usually requiring patient participation for 3 minutes (9), we
37 believe the selection of this assessment method is acceptable. We do not believe that
38 participation in the 3D-CAM up to 2 times during PACU or ICU stay will have any
39 negative effects on patient care or postoperative outcomes.
40
41

42 This study has received institutional IRB approval at Washington University School of
43 Medicine IRB ID#201612007 on December 8, 2016.
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45

46 a. Finance and insurance 47 48

49 This study involves little-to-no risk to patients, and patients will not be compensated for
50 participation. There are no relevant finance details, insurance details, or covers for
51 negligent and non-negligent harm in this study.
52
53

54 b. Reporting and dissemination 55 56

57 Results of this study will be presented at national meetings and published in a scientific
58 journal. Participants will not be individually notified regarding the results of this study.
59
60

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39 VII. Author contributions

40
41 VC and CMT contributed equally to study conceptualization, statistical design, protocol
42 drafting, and protocol editing.

43
44 VLK contributed to statistical design.

45
46 SLM completed the institutional IRB approval process.

47
48 MSA contributed to study conceptualization and protocol editing.

49 VIII. Collaborators

50
51 The authors thank Jamila Burton, Daniel Emmert, Thomas Graetz, Shelly Gupta, Tony
52 Lee, Hannah Maybrier, Angela Mickle, Maxwell Muench, Jordan Oberhaus, Ben
53 Palanca, Aamil Patel, James Spencer, Chloe Stallion, Tracey Stevens, Brian Torres,
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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.