

# BMJ Open Protocol for an observational study of delirium in the post-anaesthesia care unit (PACU) as a potential predictor of subsequent postoperative delirium

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**To cite:** Cui V, Tedeschi CM, Kronzer VL, *et al.* Protocol for an observational study of delirium in the post-anaesthesia care unit (PACU) as a potential predictor of subsequent postoperative delirium. *BMJ Open* 2017;7:e016402. doi:10.1136/bmjopen-2017-016402

► Prepublication history and additional material are available. To view these files please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2017-016402>)

Received 14 February 2017  
Revised 3 May 2017  
Accepted 22 May 2017

## 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 characterised by fluctuating course, inattention, disorganised thinking and altered level of consciousness. Delirium occurring in the hours immediately following anaesthesia 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 5 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) randomised controlled trial will be eligible for this substudy. A validated delirium assessment method, the 3-min Diagnostic Confusion Assessment Method and the Richmond Agitation and Sedation Scale will be used to assess 100 patients for delirium at 30 min and 60 min following tracheal tube removal. Patients will also be assessed for delirium over postoperative days 1–5 using three validated methods, the Confusion Assessment Method (CAM), CAM for the Intensive Care Unit 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 substudy of ENGAGES has been approved by the ethics board of Washington University School of Medicine. Enrolment began in June 2016 and will continue until June 2017. Dissemination plans include presentations at scientific conferences and scientific publications.

**Trial registration number** NCT02241655.

## INTRODUCTION

### Background and rationale

The following protocol is compliant with published guidelines for observational study protocols.<sup>1</sup> This study intends to answer the research question of whether delirium in the

## Strengths and limitations of this study

- The 3-min Diagnostic Confusion Assessment Method (3D-CAM) is a validated, appropriate method for assessment of delirium in the post-anaesthesia care unit or intensive care unit patient population at multiple time points during their stay.
- Delirium assessments at 30 and 60 min after tracheal tube removal will allow serial evaluation of the development of delirium signs over the course of the immediate postoperative period.
- This substudy has a relatively small sample size, is being conducted at only one academic medical centre, Barnes-Jewish Hospital and is a convenience sample based on surgical patients who have already consented to participation in the SATISFY-SOS study and Electroencephalography Guidance of Anesthesia to Alleviate Geriatric Syndromes trial.
- Patients may experience survey fatigue and be unwilling to complete 3D-CAM assessments at the 30 or 60 min time points, or additional delirium assessments in postoperative days 1–5.
- 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 5 subsequent postoperative days.

first hour post-tracheal tube removal, assessed in the post-anaesthesia care unit (PACU) or intensive care unit (ICU), is independently predictive of delirium on postoperative days 1–5.

Delirium is an acute, reversible disorder of attention, cognition and level of consciousness.<sup>2</sup> 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



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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 colour, as elaborated in the Aldrete score.<sup>3</sup> Approximately 80% of patients at our hospital are eligible for PACU discharge between 1 hour and 3 hours after PACU admission.<sup>4</sup> 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.<sup>5</sup> 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.<sup>6</sup> Delirium presenting in the PACU has been referred to as 'emergence delirium' and may be attributable to residual effects of general anaesthesia and should theoretically resolve within minutes to hours. Postoperative delirium, arbitrarily defined as occurring 1–5 days following surgery, may have distinct aetiologies from emergence delirium in the PACU. The relationship between delirium occurring immediately following surgery and emergency from anaesthesia 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.<sup>6–9</sup> 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 and Sedation Scale (RASS) to classify the delirium as hyperactive or hypoactive.<sup>6,10–12</sup> This study found that of the 16% of subjects found to have delirium signs during their PACU stay, when assessed at 30 min, 60 min and at discharge, 92% exhibited signs of the hypoactive subtype and 8% exhibited signs of the hyperactive subtype.<sup>6</sup> This is compared with 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.<sup>6</sup> 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.<sup>8</sup> Out of 19 episodes of postoperative delirium found, 14 (74%) had experienced emergence delirium while in the PACU.<sup>8</sup> Using the Nu-DESC (Nursing Delirium Screening Scale) assessment for delirium, a cumulative observational scoring system including disorientation, inappropriate behaviour, 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.<sup>7</sup> Of 38 patients who experienced delirium in the first postoperative day (38/862=4.2%), 32 (84.2%) had previously displayed emergence delirium.<sup>7</sup> In their population of 47 patients with hip-fracture repair, Sharma *et al* employed the unabbreviated Confusion Assessment Method (CAM) assessment at 60 min 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.<sup>9</sup>

The CAM is a validated and widely used delirium assessment instrument that is used primarily by non-psychiatrists.<sup>13</sup> Both the CAM-ICU and the 3-min Diagnostic Confusion Assessment Method (3D-CAM) are abbreviated delirium assessments derived from the CAM, with the CAM-ICU designed specifically for assessing intubated or non-verbal patients.<sup>11,12</sup> The 3D-CAM consists of a subset of the assessment components used in the CAM, designed to only take 3 min, supplemented by a series of questions regarding patient behaviour during the interview to be completed by the interviewer following the patient visit.<sup>11</sup> The major advantage of both the 3D-CAM and CAM-ICU compared with the unabbreviated CAM is 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 with the CAM.<sup>11</sup> 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% to 100%) and a 53% sensitivity for the CAM-ICU (95% CI 29% to 76%).<sup>14</sup> The 3D-CAM and CAM-ICU were both reported as having >90% specificity for detecting delirium.<sup>14</sup> Unlike the CAM-ICU, the 3D-CAM requires the patient to verbally answer questions assessing for orientation and attention. These features are emphasised in the DSM-V over altered level of consciousness, which the CAM-ICU assesses by incorporating the RASS score into its delirium assessment.<sup>11</sup> 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 postoperative 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.<sup>2</sup> 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.<sup>2</sup>

Signs of delirium such as fluctuating level of consciousness and disorganised 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 handoff 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.<sup>15</sup>

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

## 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.

## METHODS AND ANALYSIS

### Study design

This retrospective study is a substudy 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 randomised clinical trial to determine whether EEG-guided anaesthesia care can reduce the incidence of postoperative delirium and improve health-related quality of life postoperatively, when compared with usual anaesthesia 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 composed of ENGAGES participants only.

### 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 substudy, 3D-CAM assessments will be performed in the PACU or ICU at 30 min 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) disorganised 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.

### 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 OR to be approximately 3.96.<sup>6</sup> 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 OR of 3.0, along with 80% power and  $\alpha$  of 0.05, two tails and 30% discordant pairs,<sup>6</sup> the required sample size is 100 patients. Assuming 10% of patients are unable to be assessed, we will enrol 110 patients.

### 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 5 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.

### Study group and consenting process

The target population for this study comprises all patients undergoing elective surgery at Barnes-Jewish Hospital beginning 8 June 2016 and until the study enrolment 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.

### Eligibility criteria

Inclusion criteria:

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

1. Enrolled in the SATISFY-SOS study or ENGAGES study (see online supplementary appendix A)
2. Tracheal tube removal on postoperative day 0 before 19:00 hours.

### 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 anaesthesia, anaesthesia 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, and delirium assessments using the 3D-CAM will be performed at 30 min and at 60 min 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 standardised, 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 postoperative 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.

### 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.<sup>16 17</sup> 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.<sup>18</sup> The three confounders that will be included in the model are age (continuous), Short Blessed Test (continuous)<sup>19 20</sup> and Charlson Comorbidity Index (continuous).<sup>21 22</sup> Age of 65 years or older, cognitive impairment, dementia and coexisting medical conditions including multiple comorbidities, chronic renal or hepatic disease, stroke and neurological have been consistently described as risk factors for postoperative delirium.<sup>23</sup> 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.<sup>24</sup>

Coefficients to variables will be considered significant at level of  $\alpha < 0.05$ . Results will be reported as ORs with 95% CIs. We prespecify the minimum important OR for having potential predictive utility would be a  $>20\%$  change in either direction (ie, OR  $< 0.8$  or  $> 1.2$ ).<sup>25</sup> The 3D-CAM is less sensitive than the CAM for delirium detection.<sup>11</sup> 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 (ie, false-negative result).

### 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.

### Strengths and limitations

#### 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 with the CAM-ICU.<sup>9 11 14</sup>

Performing two brief assessments for delirium at time points 30 and 60 min 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.

#### Limitations

This study has several limitations. It is being conducted at only one academic medical centre, 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 min and 60 min post-tracheal tube removal as possible. However, due to logistical considerations such as patient transport and anaesthesia 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 min post-tracheal tube removal rather than at both time points. Patient responses to the 3D-CAM administered at the second time point may also be influenced by their 3D-CAM at 30 min after tracheal tube removal, that is, they may experience survey fatigue. It is also possible that participation in this study may impact a patient's willingness to continue their enrolment 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.

### 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.

### 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 min,<sup>9</sup> we believe the selection of this assessment method is acceptable. We do not believe that participation in the 3D-CAM up to two 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 no 201612007 on 8 December 2016.

## 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.

## 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.

**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.

**Contributors** VC and CMT contributed equally to study conceptualisation, statistical design, protocol drafting and protocol editing. VLK contributed to statistical design. SLM completed the institutional Institutional Review Board (IRB) approval process. MSA contributed to study conceptualisation and protocol editing.

**Funding** This work was supported by National Institute on Aging (NIA) Grants 1UH2AG050312-01 and 5UH3AG050312-03 as a substudy of ENGAGES. SATISFY-SOS was supported by Barnes Jewish Hospital (BJH) Foundation grant BJHF No 7937-77. VC was supported by NIH Training Grant 2T35HL007815-21.

**Competing interests** None declared.

**Ethics approval** IRB approval at Washington University School of Medicine IRB No. 201612007 on December 8, 2016.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data sharing statement** Data collection for this study is ongoing.

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