BMJ Open

Protocol for the Prognosticating Delirium Recovery Outcomes Using Wakefulness and Sleep Electroencephalography (P-DROWS-E) study: a prospective observational study of delirium in elderly cardiac surgical patients

S Kendall Smith ,[1] Thomas Nguyen,[1] Alyssa K Labonte,[1] MohammadMehdi Kafashan,[1] Orlandrea Hyche,[1] Christian S Guay,[1] Elizabeth Wilson,[1] Courtney W Chan,[1] Anhthi Luong,[1] L Brian Hickman,[1] Bradley A Fritz,[1] Daniel Emmert,[1] Thomas J Graetz,[1] Spencer J Melby,[2] Brendan P Lucey,[3] Yo-El S Ju,[3] Troy S Wildes,[1] Michael S Avidan,[1] Ben J A Palanca [1,4,5]

To cite: Smith SK, Nguyen T, Labonte AK, *et al*. Protocol for the Prognosticating Delirium Recovery Outcomes Using Wakefulness and Sleep Electroencephalography (P-DROWS-E) study: a prospective observational study of delirium in elderly cardiac surgical patients. *BMJ Open* 2020;**10**:e044295. doi:10.1136/bmjopen-2020-044295

► Prepublication history and supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2020-044295).

SKS and TN contributed equally.

Received 31 August 2020
Revised 30 September 2020
Accepted 05 October 2020

For numbered affiliations see end of article.

Correspondence to
Dr Ben J A Palanca;
palancab@wustl.edu

ABSTRACT

Introduction Delirium is a potentially preventable disorder characterised by acute disturbances in attention and cognition with fluctuating severity. Postoperative delirium is associated with prolonged intensive care unit and hospital stay, cognitive decline and mortality. The development of biomarkers for tracking delirium could potentially aid in the early detection, mitigation and assessment of response to interventions. Because sleep disruption has been posited as a contributor to the development of this syndrome, expression of abnormal electroencephalography (EEG) patterns during sleep and wakefulness may be informative. Here we hypothesise that abnormal EEG patterns of sleep and wakefulness may serve as predictive and diagnostic markers for postoperative delirium. Such abnormal EEG patterns would mechanistically link disrupted thalamocortical connectivity to this important clinical syndrome.

Methods and analysis P-DROWS-E (Prognosticating Delirium Recovery Outcomes Using Wakefulness and Sleep Electroencephalography) is a 220-patient prospective observational study. Patient eligibility criteria include those who are English-speaking, age 60 years or older and undergoing elective cardiac surgery requiring cardiopulmonary bypass. EEG acquisition will occur 1–2 nights preoperatively, intraoperatively, and up to 7 days postoperatively. Concurrent with EEG recordings, two times per day postoperative Confusion Assessment Method (CAM) evaluations will quantify the presence and severity of delirium. EEG slow wave activity, sleep spindle density and peak frequency of the posterior dominant rhythm will be quantified. Linear mixed-effects models will be used to evaluate the relationships between delirium severity/duration and EEG measures as a function of time.

Ethics and dissemination P-DROWS-E is approved by the ethics board at Washington University in St. Louis. Recruitment began in October 2018. Dissemination plans include presentations at scientific conferences, scientific publications and mass media.

Trial registration number NCT03291626.

Strengths and limitations of this study

- ► The Prognosticating Delirium Recovery Outcomes Using Wakefulness and Sleep Electroencephalography study is a prospective observational study conducted in a perioperative patient population burdened with a high incidence of postoperative delirium.
- ► Longitudinal delirium assessments in tandem with electroencephalography (EEG) across diverse states of arousal will provide important insight into patient trajectories throughout the perioperative period.
- ► Coupling serial delirium assessments with structured chart review may improve sensitivity for detecting delirium despite its transient and fluctuating nature.
- ► Wireless wearable EEG recording devices outfitted with dry electrodes allow for data acquisition with minimal interference in patient care; however, sensitivity to motion artefact and patient tolerance may challenge data acquisition and interpretation.
- ► Prolonged postoperative sedation in the intensive care unit may complicate the interpretation of delirium assessments and EEG.

INTRODUCTION

Postoperative delirium: a significant clinical problem

Delirium is a potentially preventable disorder with substantial negative impact on perioperative outcomes. Postoperative delirium

is associated with prolonged hospitalisation, persistent functional decline and mortality.[1–6] Moreover, this postoperative problem is part of a larger problem that costs the USA up to $152 billion annually.[7] After major cardiac and non-cardiac surgery, the incidence of delirium in elderly patients is estimated to exceed 25%.[8 9] However, the condition may be underdiagnosed. First, assessment timing and frequency may compromise detection because delirium exhibits a fluctuating course of inattention and disordered cognition. Manifestation peaks within the first two postoperative days, but variance in onset and recurrence impairs detection across individuals.[10 11] Second, without use of sensitive screening instruments, clinicians may underdiagnose the more common hypoactive delirium subtype that arises subtly as disorganised thinking and disengagement.[11–15] Finally, subsyndromal delirium may also be difficult to detect as patients may show signs without fulfilling all diagnostic criteria.[16–18] These cases are clinically impactful and have been targeted for palliative intervention due to associated poor outcomes.[17–22] Despite this, no quantitative biomarkers exist that predict delirium onset, trajectory or severity. Identifying such prognostic markers may help develop preventative or abortive therapies and may elucidate underlying neural mechanisms.

Perioperative sleep disruption: a potential contributor to delirium

Sleep addresses critical homoeostatic needs for restoring physiological processes such that deficiencies result in cognitive decrements and immune and endocrine system impairments.[23–25] Acute sleep deprivation is linked to increases in oxidative stress, increased blood brain barrier permeability and reduced clearance of extracellular metabolites—all putative mechanisms underlying postoperative delirium.[26] Furthermore, chronic sleep disorders are prevalent in neurodegenerative disorders including Alzheimer's disease (AD) and may increase delirium susceptibility.[6 27 28] Advanced age is also associated with sleep disorder prevalence,[29] which may increase delirium susceptibility in older adults. In the perioperative arena, preliminary actigraphy studies suggest an association between abnormal sleep–wake cycle patterns and postoperative delirium.[30–32] These studies have not been followed by large-scale investigations of brain activity to examine the relationship between sleep structure and delirium outcomes. This is important because sleep may be a modifiable contributor to postoperative delirium.

Polysomnography (PSG), the gold-standard for studying sleep, requires patients to be tethered to amplifiers and acquisition computers. This hindrance to patient comfort and postoperative rehabilitation has limited perioperative studies of sleep. PSG relies on electroencephalographic (EEG) waveforms to detect wakefulness and classify sleep into distinct stages of rapid eye movement (REM) and non-rapid eye movement (NREM) sleep.[33] These stages, interspersed in cycles throughout sleep, are defined by well-known EEG waveforms and corresponding physiological processes (figure 1A). For instance, sleep spindles can occur in stage N2 sleep, which comprises approximately 50% of total sleep time. The presence of EEG slow waves defines stage N3 sleep, which is associated with restorative physiological benefits across multiple organ systems.[34–36] These EEG waveforms facilitate segmentation into sleep stages and have characteristics in the frequency domain (figure 1B).

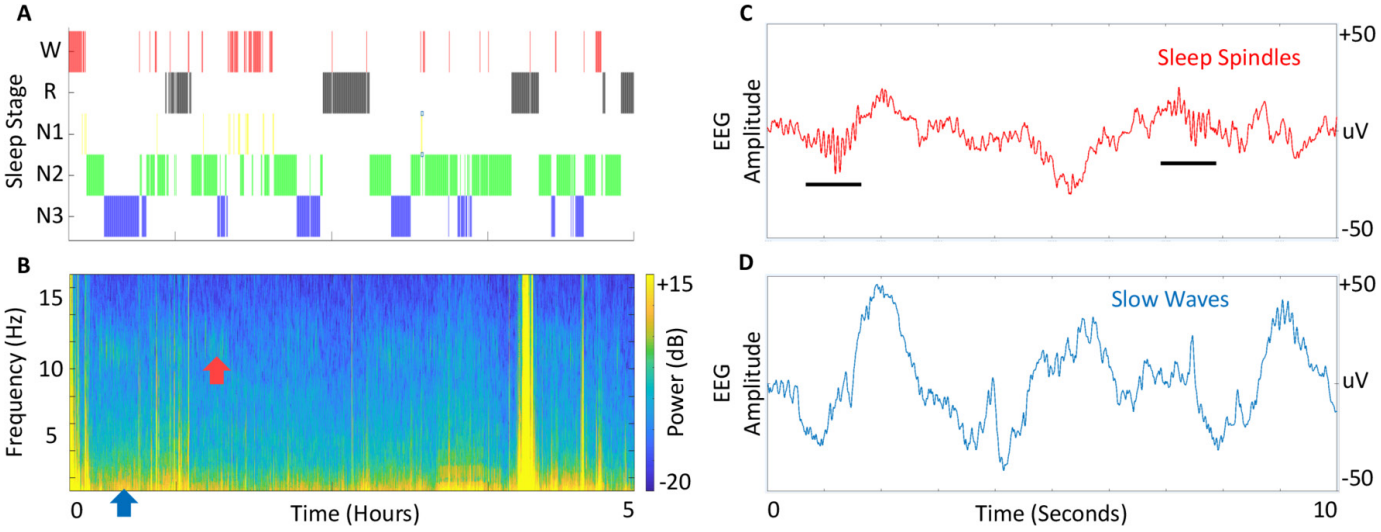

Figure 1 Overnight electroencephalography (EEG). A hypnogram acquired with the EEG device reveals cycling of sleep stages over an evening with wakefulness (W), rapid eye movement sleep (R) and non-rapid eye movement sleep stages (N1, N2 and N3) (A). The corresponding spectrogram shows signal power in the frontal EEG decomposed by frequency as a function of time. Slow waves (blue arrow) carry low frequency power during N3 sleep, while sleep spindles (red arrow) have power in higher frequencies and occur primarily during N2 sleep (B). Sleep spindles (underlined) occurring at the point designated by the red arrow in panel B are reflected by ~13 Hz power (C). Slow waves occurring at the point designated by the blue arrow in (B) are reflected by 0.5–4 Hz power (D).

Despite technical limitations, small studies have demonstrated profound postoperative changes in sleep architecture with unknown clinical implications. N3 sleep suppression occurs on the day of anaesthesia in volunteer studies and persists on subsequent postoperative nights.[37 38] Fragmentation of sleep architecture and overexpression of N2 with reduction of N3 and REM sleep occur in the first postoperative night following both cardiac and non-cardiac surgery.[38–45] N3 and REM sleep return on the third or fourth postoperative nights.[32 38 43 46] However, the clinical impact of NREM sleep disruption remains unclear as EEG waveforms defining different sleep stages have not been related to postoperative delirium or other perioperative outcomes.

EEG markers of sleep and wakefulness and thalamocortical disruption

Sleep stages, characterised by EEG waveform morphology, are normally regulated by circadian and sleep homoeostatic processes.[47 48] Preliminary studies in critically ill, ventilated patients with delirium have revealed abnormal EEG waveform characteristics corresponding to sleep–wake states. For instance, sleep spindles are absent during phenotypic sleep while slow waves are present during apparent wakefulness.[49 50] Taken together, these data suggest that investigating EEG during perioperative sleep and wakefulness may aid in correlative studies on the time course of delirium onset.

Sleep spindles

Originally described by Loomis *et al*,[51] EEG sleep spindles reflect thalamocortical connectivity for sustaining sleep and consolidating memory.[52] These oscillations in N2 and N3 sleep (reviewed in Loomis *et al*[53]) originate from the thalamic reticular nucleus and propagate across the cortex with differential expression patterns in occipital and frontal EEG.[54 55] Sleep spindles possess a waxing and waning pattern of at least 0.5 s in duration (figure 1C). Within an individual, the dominant frequency of sleep spindles in the 9–16 Hz range is conserved.[56] Sleep spindle expression is under inverse homoeostatic control with a reduction in density following acute sleep deprivation.[57] Sleep spindle density, calculated as the number of spindles per unit time, varies over an evening of sleep.[58 59] This measure may be a useful marker of chronic sleep deprivation and cognitive dysfunction; decrements mirror the severity of cognitive episodic memory dysfunction in AD patients.[58 60] Furthermore, abnormal sleep spindle expression occurs in patients with severe dementia and schizophrenia and is predictive of dementia in patients with Parkinson's disease years after measurement.[61–64] Analogues of sleep spindles are observed during sedation and general anaesthesia with an unknown impact on subsequent homoeostatic regulation and expression.[65–67] Overall, perioperative sleep spindle expression has not been characterised or related to perioperative outcomes.

Slow wave activity

Sleep slow waves are characteristic of N3 sleep and may be useful for tracking cognitive function.[68] They are putative markers of synaptic pruning, memory consolidation and have been related to the clearance of beta-amyloid and other metabolites.[69–72] Sleep slow waves are defined through high amplitude, low frequency oscillations on EEG (figure 1D). In order to correlate cognitive function with low frequency oscillation amplitude, sleep slow wave activity (SWA) is calculated as the total EEG power of contributory low frequencies (eg, 1–4 Hz) per minute.[73 74] Regional sleep SWA positively correlates with learning and subsequent visuomotor task performance[75] that may be impaired by auditory interventions.[76] Exogenous enhancement of SWA potentiates memory and task performance.[77] In contrast, selective acute SWA deprivation induces a rebound in magnitude on the next day based on the preceding deficit.[78–80] Furthermore, reduced SWA is associated with beta amyloid deposition, tau pathology,[81] atrophy in prefrontal cortical regions and impaired memory.[71 82]

In adults, slow waves observed during wakefulness[83–86] are usually associated with underlying structural or functional pathology.[87] Moreover, diffuse slow waves may represent disrupted thalamocortical connectivity.[88] Previous work has identified slow waves during apparent wakefulness in patients with postoperative delirium.[89–91] Furthermore, low EEG frequency predominance has been reported as a non-specific marker of hepatic encephalopathy,[92–95] sepsis-associated encephalopathy[96–99] and postoperative delirium.[89 90 100–109] Slow waves are associated with altered thalamocortical connectivity during general anaesthesia.[110] Whether overexpression of slow waves during wakefulness precedes postoperative delirium remains unknown.

Posterior dominant rhythm

The posterior dominant rhythm (PDR) is a robust marker of thalamocortical connectivity, integrity and cognitive function during relaxed wakefulness with eyes closed.[33 111 112] The PDR consists of oscillations evoked by eyelid closure that have greatest amplitude in occipital EEG derivations.[112 113] For the vast majority of adults, the dominant frequency of the PDR lies within the 8–13 Hz (alpha) frequency band (figure 2). Lower PDR frequencies observed in AD patients are associated with thalamic deficiencies of norepinephrine.[114 115] Similarly, low PDR frequencies during apparent wakefulness have shown promise as a marker of early and advanced cognitive impairment of AD.[116–120] The severity of slowing appears to correlate with the degree of cognitive impairment[121–125] but has not been evaluated longitudinally in the perioperative period.

Hypotheses and aims

We hypothesise that delirium is a disorder of both sleep and wakefulness resulting from abnormal thalamocortical connectivity. Furthermore, we hypothesise that

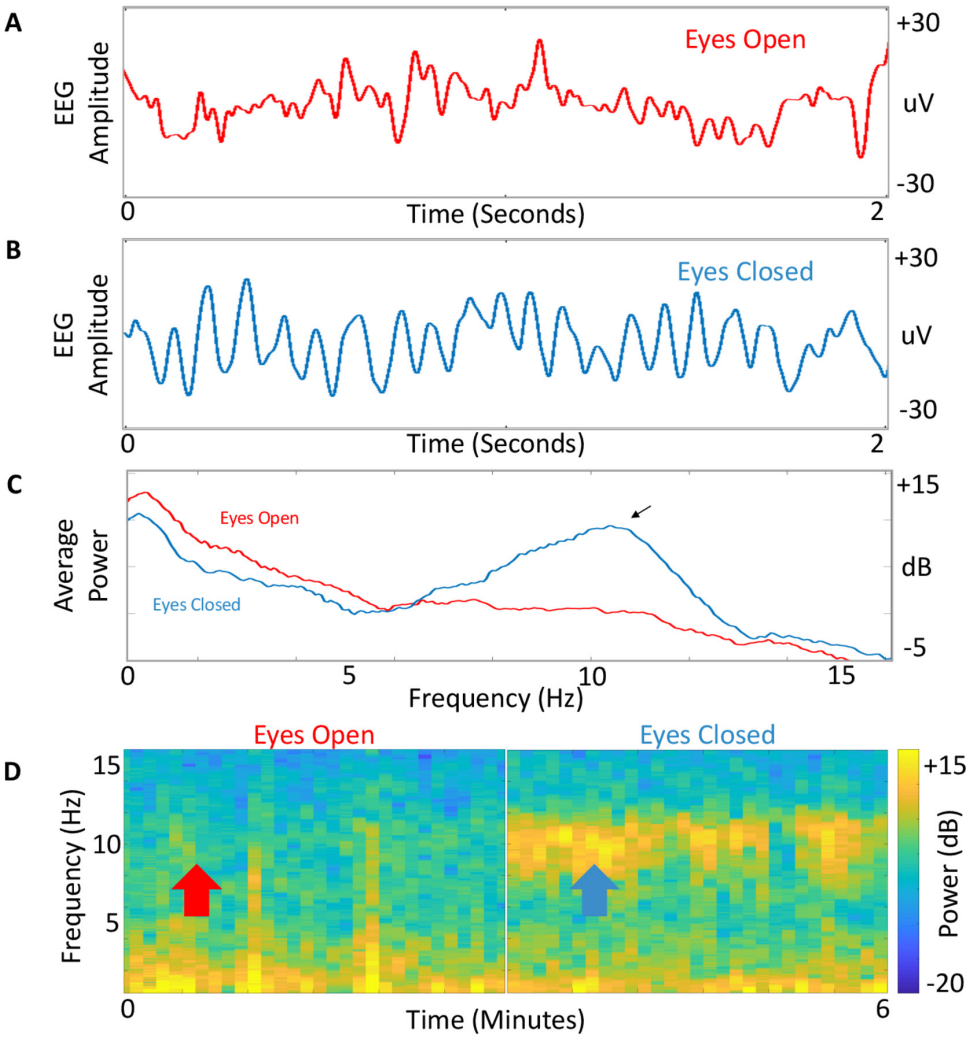

Figure 2 The posterior dominant rhythm (PDR) during eyes closed wakefulness using the electroencephalography (EEG) recording device. Alpha oscillations are not easily discernable during eyes open wakefulness (A). During eyes closed wakefulness, the PDR in cognitively intact adults is comprised oscillations in the alpha (8–13 Hz) frequency band (B). This activity is apparent in the decomposition of these two signals into power at corresponding frequencies by spectral analysis. The PDR emerges during eyes closed wakefulness with signal power at ~10 Hz (blue) compared with signal power during eyes open (red) (C). A power spectrogram demonstrates quantifiable fluctuations in the ~10 Hz power during epochs of eyes open vs eyes closed wakefulness (red vs blue arrow) (D).

EEG alterations can predict delirium onset and severity. Our specific aims include the following: (1) evaluate whether preoperative EEG measures of sleep and wakefulness predict postoperative delirium and its severity; and (2) assess whether postoperative abnormalities in EEG measures of sleep and wakefulness correlate with delirium onset, severity and clinical course. For our first aim, we hypothesise that the EEG power of preoperative sleep slow waves, sleep spindle density and PDR frequency will correlate negatively with the peak severity of postoperative delirium. Our second aim, focused on postoperative findings, addresses three hypotheses: (1) delirium onset and peak severity will correlate with an increase in SWA and diminished PDR frequency during wakefulness; (2) delirium onset and peak severity will correlate with the reduction in postoperative sleep spindle density relative to preoperative measurements; (3) delirium recovery will coincide with a reversion of the dominant PDR frequencies toward preoperative values.

METHODS

Research design overview

Prognosticating Delirium Recovery Outcomes Using Wakefulness and Sleep Electroencephalography (P-DROWS-E) is a prospective longitudinal cohort observational investigation. The Human Research Protection Office at Washington University School of Medicine approved the study in 2017. P-DROWS-E was registered prior to enrolment and conforms to the Standard Protocol Items: Recommendations for Interventional Trials checklist (see online supplemental file 1).

Study participants

We will enrol 220 patients undergoing elective cardiac surgery at Barnes-Jewish Hospital, St. Louis, Missouri. Inclusion criteria are (1) English-speaking, (2) age 60 years or older and (3) undergoing elective major cardiac surgery requiring cardiopulmonary bypass (eg, coronary artery bypass grafting, aortic repair/replacement, septal myectomy, Maze procedure and/or heart valve repair/replacement). Exclusion criteria are (1) undergoing surgery requiring deep hypothermic circulatory arrest, (2) pre-existing delirium, defined by a positive preoperative confusion assessment method (CAM) evaluation and (3) inability to participate sufficiently in delirium screening due to deafness, blindness or poor English fluency. We minimised exclusion criteria to maximise generalisability of findings to the general cardiac surgical population. Participants will be compensated for their efforts: $50 for each preoperative EEG recording and $25 for each intraoperative and postoperative EEG recording, up to $300.

Recruitment

Recruitment and enrolment of eligible patients will occur following screening of the cardiac surgery schedule at Barnes-Jewish Hospital, the Center for Preoperative Assessment and Planning clinic schedule, and inpatient census lists from cardiology and cardiothoracic wards by study coordinators.

Data collection

Preoperative screening and assessment tools

Baseline sleep–wake function will be evaluated through questionnaires including daytime sleepiness with the Epworth Sleepiness Scale,[126] overall sleep–wake function with the Patient Reported Outcomes Measurement Information System (PROMIS) Sleep Related Impairment/Sleep Disturbance Scale,[127] sleep quality with the Pittsburgh Sleep Quality Index[128] and obstructive sleep apnoea risk estimation with the Snoring, Tiredness, Observed apnea, high blood-Pressure, BMI, Age, Neck circumference, and male Gender (STOP-BANG) questionnaire.[129]

Baseline depression, cognition and prior education are prognostic factors for postoperative delirium. Therefore, patients will complete the Geriatric Depression Scale short form[130] and the Montreal Cognitive Assessment, which screen for cognitive impairment.[131] In addition, the AD-8,[132] a rapid screen that has been validated against AD biomarkers, will be used.[133] The number of years of education will also be recorded. Finally, the CAM[134] and serial pain assessments will be performed.

Confusion assessment method

The CAM is used to diagnose delirium based on five key domains: (1) acute onset, (2) fluctuating course, (3) inattention, (4) disorganised thinking and (5) altered level of consciousness.[134] It is a validated tool for delirium diagnosis with a sensitivity of 94% and specificity of 89% against full neuropsychiatric evaluation.[135] CAM administration takes 10–20 min at our institution and consists of a formal patient interview comprised questions that identify delirium symptoms and test cognition.

CAM assessments will be performed by researchers who have undergone an established rigorous training process.[136 137] All assessments will be independently reviewed by a separate, trained research team member for internal scoring consistency and completeness. Ambiguous assessments will be reviewed by the research team and PI weekly with concomitant adjudication of each domain and the overall delirium determination. The patient's family and nurse are also questioned about the patient's postoperative mental status as needed. Patients whose medical condition prohibits the use of the CAM will be assessed using the CAM for the intensive care unit (CAM-ICU) instrument.[138 139] Both the CAM-ICU and the CAM have been shown have good agreement with the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV criteria for delirium.[140–142]

Pain assessments

A limited number of studies suggest an association between acute postoperative pain and delirium.[143–145] Therefore, serial pain evaluations will be completed using the Behavioral Pain Scale (BPS)/BPS Non-Intubated and the Visual Analog Scale.[146] Evaluations will be performed after each CAM assessment.

EEG apparatus

Perioperative EEG will be used to assess markers of wakefulness, sleep and delirium. To address the technical limitations of PSG, we will employ a consumer-grade wearable wireless EEG device (Dreem, Rhythm, New York, New York, USA) requiring minimal clinical intervention and maintenance (figure 3A).[147 148] It yields continuous multichannel EEG data through dry electrodes, heart rate through infrared detectors and head movement through accelerometers. In addition to frontal forehead sensors (F7, F8 and Fpz), occipital EEG signals are acquired using posterior sensors (O1 and O2). Adequate signal quality will be assessed by research staff.

Preoperative EEG acquisition

To maximise patient compliance and signal quality, research staff will demonstrate wireless EEG device usage. Patient head circumference will be measured, and the device will be adjusted for proper fit. To obtain baseline PDR, patients will be asked to remain still and relaxed for 4 min with eyes open followed by a 4 min period of eyes closed (figure 3B). Patients will demonstrate comprehension by donning the device and initiating a recording themselves.

Patients will be requested to wear the device for up to two nights before surgery to allow for EEG sleep structure assessment. For inpatients, research staff may assist with device application. For outpatients, the device, charger, alcohol wipes, an educational video and an instruction sheet will be provided. Research staff will also be available

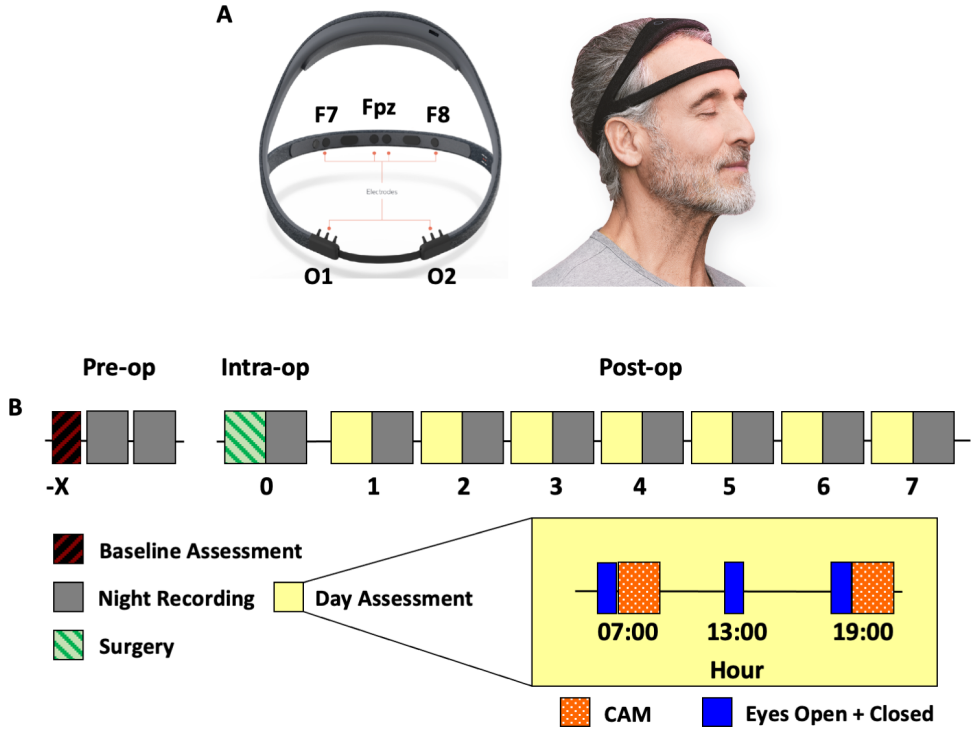

Figure 3 Overview of electroencephalography (EEG) device and patient participation workflow. Perioperative EEG will be obtained via the Dreem device, a consumer-grade wireless wearable EEG device that records from five sensors, pulse oximetry and accelerometry (A). Longitudinal assessments of EEG and delirium symptomatology will occur preoperatively, intraoperatively and postoperatively. Following consent in the Center for Preoperative Assessment and Planning/inpatient unit, a baseline confusion assessment method (CAM) and EEG are acquired. Postoperative daytime assessments occur within a 2-hour window surrounding 07:00, 13:00 and 19:00 until postoperative day 7, patient withdrawal or hospital discharge (B). The human in this figure is a model and not a patient. Permission was granted for non-commercial use of this image by Dreem.

by phone to address questions. Patients will be contacted by phone to ensure compliance, satisfaction and data quality.

Day of surgery EEG acquisition

If necessary, additional preoperative awake EEG data will be obtained. The Dreem will then be used throughout anaesthetic induction, maintenance and emergence (figure 3B). Research staff will optimise EEG acquisition through device adjustments, as needed.

Postoperative EEG acquisition, delirium assessments and pain scores

Semi-continuous EEG recordings will be acquired up to postoperative day (POD) 7, patient withdrawal or hospital discharge (figure 3B). To enhance data collection, participants will be asked to wear the device within 2 hours of 07:00, 13:00 and 19:00 for 4 min each during eyes open and eyes closed periods. The 07:00 and 19:00 recording sessions will coincide with acquisition of CAM and pain scores. CAM-ICU will be used for intubated patients.[149] EEG but not CAM data will be obtained for unresponsive patients (Richmond Agitation-Sedation Scale (RASS)[150] level −4 or −5). Participants will wear the device overnight to provide data on nocturnal sleep structure.

Structured chart review for delirium

Coupling structured chart review with CAM/CAM-ICU increases sensitivity in detection of delirium without loss of specificity.[151 152] Therefore, formal structured chart reviews will be performed by independent trained clinical researchers who are blinded to EEG and CAM data. Reviews will occur daily until POD 7. The chart review methodology (table 1) will use patient information from the electronic medical record including mental status, progress notes, medication usage (including psychotropic, sedative and pain medications) and relevant clinical details (eg, length of stay, ICU behavioural interventions, extubation and/or re-intubation procedures, etc).[151 152] Structured chart review training will be adapted from previously published methods,[152] and only CAM trained staff will be eligible. In cases where chart review delirium outcome is uncertain, a consensus review will occur. In cases where chart review is discordant with both CAM assessments on a given day, a formally trained attending clinician blinded to all other metrics will determine the final outcome.

Analyses

EEG preprocessing and analysis

EEGLAB,[153] an open-source analytical suite for MATLAB (Mathworks, Natick, Massachusetts, USA), will be used

Table 1 Chart abstraction for delirium during hospitalisation

Was delirium diagnosed by a clinical provider? (*Review diagnosis code summary in electronic medical record for any diagnoses related to delirium*.)	► Yes ► No ► Uncertain
Was there any evidence in the chart of acute confusion (eg, delirium, mental status change, disorientation, hallucinations, agitation, etc)? (*Review all handwritten and electronic notes, flowsheet data, and documented CAM-ICU results performed twice daily by nursing staff*.)	► Yes ► No ► Uncertain
Was there any documentation of the use of delirium prevention strategies at any time during the hospitalisation before delirium occurred? (*Review flowsheet data for nursing interventions such as reorienting patient to room, equipment, unfamiliar surroundings, person, situation, time and adjustment of lighting during day*.)	► Yes ► No ► Uncertain
Was there any documentation of the use of a restraint or bed alarm/device recorded during the patient's stay? (*Review flowsheet data for documentation of any restraint devices used*.)	► Yes ► No ► Uncertain
Outcome By chart review, delirium was	► Present ► Absent ► Uncertain ► Cannot be determined

Outcome is determined after a complete review of the medical record. Questions 1–4 are designed to help the reviewer identify evidence of delirium consistent with diagnostic criteria including an acute change or fluctuating course, inattention and disorganised thinking or altered level of consciousness.
CAM-ICU, confusion assessment method for the intensive care unit.

for down-sampling deidentfied EEG to 128 Hz after band-pass filtering (0.1–50 Hz first order Butterworth). Records will undergo visualisation and artefact removal using EEGLAB plugins and/or custom-coded MATLAB scripts. Multitaper methods will be used for power spectral analysis using the MATLAB Chronux toolbox.[154] Spectral estimates between 0.5 and 30 Hz will be based on 6 s non-overlapping time windows, time-bandwidth product of 3 and 5 tapers.

Sleep technologist scoring

Records will undergo sleep staging with visualisation in Philips Respironics Sleepware G3 Software. They will be scored successively with a low frequency filter (LFF) of 1 Hz then 0.3 Hz and a high frequency filter of 30 Hz. The LFF of 1 Hz will attenuate artefacts related to sweat, respiration and movement. Rescoring with an LFF of 0.3 Hz will allow for best quantification of SWA and stage N3 sleep. Channels Fpz-F8, Fpz-F7 and F8-F7 will be used for visual scoring, while occipital derivations will be used secondarily. Additionally, accelerometer channels will be used to identify movement, respiratory patterns and arousals. Registered polysomnographic technologists will score the record in 30 s epochs using the modified American Association of Sleep Medicine (AASM) criteria (table 2).[33] Evaluators will be blinded to delirium clinical outcomes and automated scoring provided by the manufacturer.

Quantitative measures of sleep spindle and slow waves

Sleep spindles will be scored manually by registered polysomnographic technologists using AASM guidelines and with the assistance of publicly available algorithms implemented in our laboratory.[63 155–162] Spindle density will be computed from the number of spindles per minute of N2 and N3 sleep. Dissipation in sleep spindle power (ie, total power across 11–16 Hz) will be assessed over the course of nocturnal sleep.

Custom-written MATLAB subroutines will compute the SWA as the total absolute spectral power in the 1–4 Hz frequency band, calculated in 1 min intervals during N2 and N3 sleep.[163] Custom-written MATLAB code will be used to detect individual slow waves and calculate their power.[164] For our second aim, predictor SWA measurements during phenotypic wakefulness will be computed from postoperative recordings where EEG slowing is noted despite persistent criteria for wakefulness (eg, eye movements, high frequency activity (>30 Hz) and motion artefact). Registered sleep technologists will review these expected discordant epochs.

Quantitative measures of the PDR

Previously developed MATLAB scripts will be used to quantify PDR frequency from EEG recorded during eye closure. Registered sleep technologists will first screen the occipital EEG (Fpz-O1, Fpz-O2, O1-O2) recorded during eyes closed wakefulness (07:00, 13:00 and 19:00) to identify recording contamination by sleep. Band-pass filtering of the signals will then occur, and spectral estimates will be generated through the Chronux toolbox modules.[154] PDR frequency will be determined based on peak power.

Table 2 Modified American Association of Sleep Medicine scoring criteria for different sleep stages

Stage	Criteria/description
W	**>50% epoch contains any of the following** Posterior dominant rhythm: 8–13 Hz EEG oscillations over occipital region with eyes closed Eye blinks: vertical eye movements of 0.5–2 Hz Slow eye movements: conjugate, sinusoidal eye movements Rapid eye movements: conjugate, irregular, sharply peaked eye movements
N1	**Posterior dominant rhythm absent with any of the following** Low amplitude mixed frequency EEG: 4–7 Hz activity Vertex sharp waves: EEG sharp waves with duration <0.5 s Slow eye movements: conjugate, sinusoidal or slow eye movements
N2	**Either present during the first half of an epoch or last half of previous epoch** K-complexes: EEG negative sharp wave and positive component with total duration >0.5 s and without arousal Sleep spindles: crescendo-decrescendo EEG oscillatory pattern with frequency 11–16 Hz and duration of 0.5–3 s
N3	**Presence over >20% of an epoch** EEG slow waves: delta waves with a frequency 0.5–4 Hz and peak-to-peak amplitude >60 µV
R	**All of the following present** Low amplitude mixed frequency EEG: 4–7 Hz EEG activity without K-complexes or sleep spindles Sawtooth waves: EEG train of sharply contoured or triangular waves with frequency of 2–6 Hz Rapid eye movements: conjugate, irregular, sharply peaked eye movements
NS	Epoch cannot be scored due to excessive artefact and/or inability to fulfil criteria for above stages

EEG, electroencephalography.

Processing of delirium outcomes

Daily delirium incidence will be coded as a binary variable defined by a positive CAM assessment and/or chart review. Delirium duration will be coded as a categorical variable defined by the total number of days with a positive delirium outcome, ranging from 0 to 7. Delirium subtype (hypoactive, hyperactive or mixed), based on the RASS and the CAM, will also be noted. Delirium severity will be quantified using the CAM-S and/or CAM-ICU 7. The CAM-S is a validated weighting of CAM sub-scores,[165] with a long-form version ranging from 0 to 19. The CAM-ICU-7[166] is a validated weighting of the CAM-ICU subscore ranging from 0 to 7. Raw severity scores will be normalised by the maximum score of the tool in order to yield scaled severity scores ranging from 0 to 1. The maximum scaled delirium severity score will be coded as a continuous variable in analytical models.

Statistical analyses

Linear mixed effects models will be used to evaluate relationships between EEG measures and delirium severity and duration. For our first aim, principal independent variables will include preoperative measures of sleep spindle density, sleep SWA for stages N2 and N3, and PDR frequency. For our second aim, independent variables will include EEG changes relative to preoperative baseline for sleep spindle density, awake SWA and PDR frequency. Given that EEG measures may vary by age[167–169] and sex,[163 170] these factors will be included as relevant biological variables. Secondary analytical models will include relevant medications and comorbidities such as obstructive sleep apnea and depression as well as years of education. Additional covariates to account for intraoperative anaesthetic exposure will use intraoperative measures of SWA, sleep spindle density and burst suppression[171–173] derived from intraoperative EEG device recordings. As we expect that only 25% of our patients may develop postoperative delirium, we will consider zero-inflated models.

Sample size calculations

Considering the heterogeneity of delirium phenotype and variable exposure to narcotics and other medications, we expect a large sample size to reduce the risk of completing an underpowered study. Based on preoperative recruitment of 220 patients, we expect 95% capture rate for preoperative and intraoperative recordings, and a 25% incidence of delirium based on results from the Electroencephalography Guidance of Anesthesia to Alleviate Geriatric Syndromes (ENGAGES) study,[173] with the majority completing delirium assessments throughout the postoperative period. We expect at least 70% of these patients to provide usable postoperative EEG. We anticipate the ability to capture at least moderate effects (effect size 0.5, beta 0.2, power 0.8) based on conventions for statistical power analysis in the behavioural sciences.[174]

Prespecified substudies

Other physiological markers for predicting delirium outcomes

Additional physiological markers (accelerometry, blinks and heart rate measurements), and sleep EEG markers, including N1 vertex waves, N2 K-complexes and REM sawtooth waves will be evaluated against delirium outcomes.

Device validation for elderly patients

This substudy will compare Dreem data and PSG in the geriatric population to complement early studies across a broad age.[148]

Postoperative cognitive trajectories

This substudy uses a modified version of the Brief Test of Adult Cognition by Telephone to determine the rate of postoperative cognitive recovery and how delirium impacts cognitive recovery via interval assessments up to 6 months after surgery.[175 176] The battery will evaluate multiple cognitive domains including episodic memory, working memory, processing speed, attention and executive function. Associations between EEG measures and cognitive function will also be evaluated.

Automated sleep staging

Staging provided by the manufacturer's automated algorithm will be compared with the manual sleep staging performed by registered PSG technologists.

Relationship of sleep structure to clinical outcomes

Preoperative EEG/sleep measures, sleep surveys (Epworth Sleepiness Scale, STOP BANG) and Geriatric Depression Scale scores will be evaluated against secondary postoperative clinical outcomes, including 30-day mortality, ICU length of stay, depression, atrial fibrillation and acute and persistent pain scores.

Comparisons of sleep and sleep-like EEG markers

Within-subject comparisons will be made between EEG markers spanning different states of arousal.

Utility of intraoperative EEG markers

Intraoperative EEG measures, including burst suppression will be evaluated against postoperative outcomes.

DISCUSSION

The P-DROWS-E study aims to enhance our understanding of perioperative delirium. We will use EEG recordings acquired across different states of arousal in tandem with serial perioperative delirium assessments to determine temporal associations between EEG markers and postoperative delirium outcomes. Our work is enhanced by integrating additional data including assessments of cognition and clinical variables (figure 4). As a result, we are well positioned to develop analytical models for predictive and diagnostic EEG markers of postoperative delirium.

Until recently, technical limitations have impeded incisive probing of the relationships between sleep architecture and postoperative delirium. Our study uses a battery-operated, portable device that is specifically designed for continuous long-term EEG recordings with minimal need for direct assistance by staff. This approach should greatly enhance patient participation, tolerance and comfort while posing minimal interference to postoperative sleep and rehabilitation. The EEG

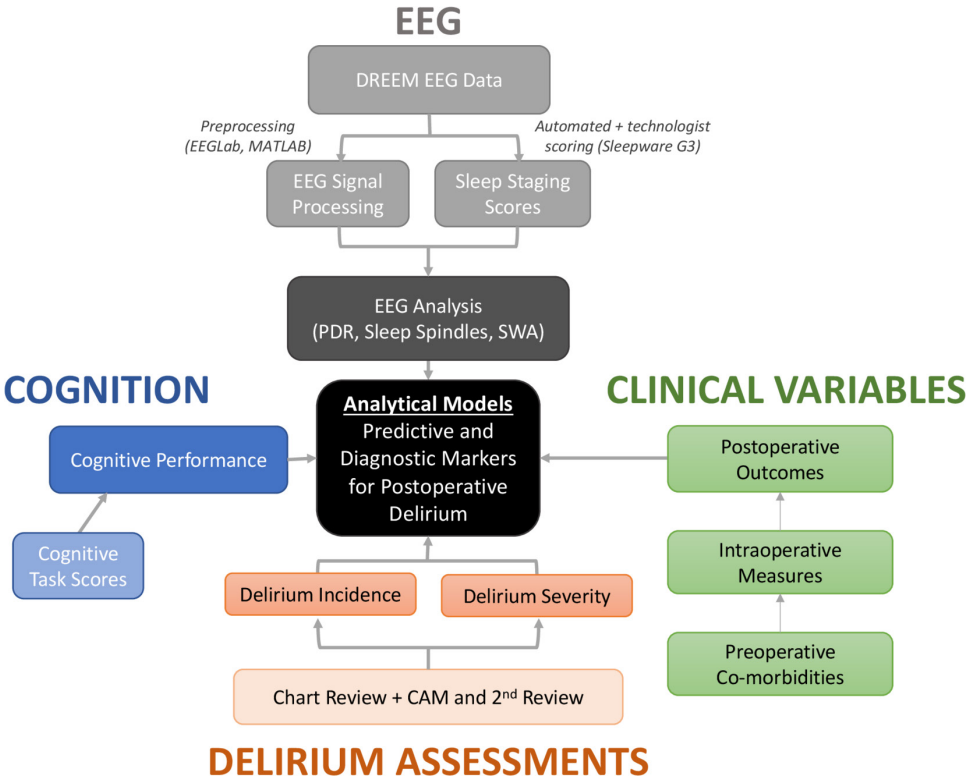

Figure 4 Prognosticating Delirium Recovery Outcomes Using Wakefulness and Sleep Electroencephalography study overview. CAM, confusion assessment method; EEG, electroencephalography; PDR, posterior dominant rhythm; SWA, slow wave activity.

device, however, is not without limitations. Dry electrodes allow comfort and easy instrumentation, but they may be more prone to artefacts related to poor skin adherence. Thus, expertise and vigilance are required to differentiate EEG waveforms from artefact to fulfil the promise of this technological advance for large scale clinical sleep investigations. Another potential confounder for EEG interpretation and delirium outcomes includes the use of anaesthetics and opioids that may contribute poorly controlled sample variance in our study population. Nevertheless, P-DROWS-E will be an important early step in identifying prognostic associations between EEG and postoperative delirium.

Application of findings and future directions

P-DROWS-E may yield EEG applications that are significant and far-reaching. The potential to better identify patients at risk for postoperative delirium and track their disorder quantitatively would advance perioperative and critical care medicine. The study also has important mechanistic implications for modulating sleep and wakefulness that have bearing on sedation and analgesic strategies in procedural medicine. Finally, the use of wireless wearable devices for monitoring brain activity is proof-of-principle for implementing neural telemetry in vulnerable populations in the future.

ETHICS AND DISSEMINATION

The study design, study procedures and informed consent procedure were approved by the ethics board at Washington University, and the study will be carried out in compliance with the Declaration of Helsinki. All participants will provide informed consent (see online supplemental file 2).

Any protocol modifications, which may impact study procedures, administrative aspects or patient safety, will require a formal amendment to the protocol. Such amendments will be approved by the Institutional Review Board prior to implementation. The study will not have a data monitoring committee given that we do not anticipate severe adverse events and was not required for our study by the Institutional Review Board. To ensure the conduct of quality research, the Washington University School of Medicine IRB regularly conducts audits of research studies. Dissemination plans include presentations at scientific conferences, scientific publications and mass media.

Author affiliations
[1]Department of Anesthesiology, Washington University in Saint Louis School of Medicine, Saint Louis, Missouri, USA
[2]Department of Surgery, Washington University in Saint Louis School of Medicine, Saint Louis, Missouri, USA
[3]Department of Neurology, Washington University in Saint Louis School of Medicine, Saint Louis, Missouri, USA
[4]Department of Biomedical Engineering, Washington University in St Louis, Saint Louis, Missouri, USA
[5]Division of Biology and Biomedical Sciences, Washington University in St Louis, Saint Louis, Missouri, USA

Acknowledgements The authors thank the additional members of the P-DROWS-E study group, including Jacob D Bolzenius, Emma R Huels, Amrita Aranake-Chrisinger, Jordan Oberhaus, Hersh Maniar, Daniel Park, Katie Dalton, Paul Galgani, Paul Krucylak and ShiNung Ching.

Contributors Authorship for this study was given to key personnel involved in study design, recruitment, data collection, data analysis. There are no publication restrictions and no professional writers were involved in the generation of the manuscript. BJAP, SKS, TN, AKL, MMK, OH, CSG, EW, BAF, DE, TJG, SJM, BPL, Y-ESJ, TSW and MSA are responsible for conceptualising study design. TN, AKL, MMK, OH, EW, CWC, AL, LBH, DE and TJG are responsible for recruitment, enrolment, data collection and/or editing the protocol. BJAP is responsible for drafting the protocol. All authors including BJAP, SKS, TN, AKL, MMK, OH, CSG, EW, CWC, AL, LBH, BAF, DE, TJG, SJM, BPL, Y-ESJ, TSW and MSA have critically revised the P-DROWS-E protocol manuscript and have approved the final version to be published. All authors agree to be accountable for the accuracy and integrity of all aspects of the P-DROWS-E study.

Funding The P-DROWSE study has been awarded funding by the National Institute on Aging (PI: Ben Palanca; award reference number: National Institutes of Health R01AG057901).

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; peer reviewed for ethical and funding approval prior to submission.

ORCID iDs
S Kendall Smith http://orcid.org/0000-0003-0718-1150
Ben J A Palanca http://orcid.org/0000-0001-7535-5701

REFERENCES

1 MacLullich AMJ, Beaglehole A, Hall RJ, *et al*. Delirium and long-term cognitive impairment. *Int Rev Psychiatry* 2009;21:30–42.
2 Jackson JC, Gordon SM, Hart RP, *et al*. The association between delirium and cognitive decline: a review of the empirical literature. *Neuropsychol Rev* 2004;14:87–98.
3 Rudolph JL, Inouye SK, Jones RN, *et al*. Delirium: an independent predictor of functional decline after cardiac surgery. *J Am Geriatr Soc* 2010;58:643–9.
4 Gottesman RF, Grega MA, Bailey MM, *et al*. Delirium after coronary artery bypass graft surgery and late mortality. *Ann Neurol* 2010;67:338–44.
5 McKhann GM, Grega MA, Borowicz LM, *et al*. Encephalopathy and stroke after coronary artery bypass grafting: incidence, consequences, and prediction. *Arch Neurol* 2002;59:1422–8.
6 Fong TG, Davis D, Growdon ME, *et al*. The interface between delirium and dementia in elderly adults. *Lancet Neurol* 2015;14:823–32.
7 Leslie DL, Marcantonio ER, Zhang Y. One-Year health care costs associated with delirium in the elderly population. *Arch Intern Med* 2008;168:27–32.
8 Dasgupta M, Dumbrell AC. Preoperative risk assessment for delirium after noncardiac surgery: a systematic review. *J Am Geriatr Soc* 2006;54:1578–89.
9 Brown CH. Delirium in the cardiac surgical ICU. *Curr Opin Anaesthesiol* 2014;27:117–22.

10 Eide LSP, Ranhoff AH, Fridlund B, *et al*. Comparison of frequency, risk factors, and time course of postoperative delirium in octogenarians after transcatheter aortic valve implantation versus surgical aortic valve replacement. *Am J Cardiol* 2015;115:802–9.
11 Robinson TN, Raeburn CD, Tran ZV, *et al*. Postoperative delirium in the elderly: risk factors and outcomes. *Ann Surg* 2009;249:173–8.
12 Nicholas LM, Lindsey BA. Delirium presenting with symptoms of depression. *Psychosomatics* 1995;36:471–9.
13 Spiller JA, Keen JC. Hypoactive delirium: assessing the extent of the problem for inpatient specialist palliative care. *Palliat Med* 2006;20:17–23.
14 van Eijk MMJ, van Marum RJ, Klijn IAM, *et al*. Comparison of delirium assessment tools in a mixed intensive care unit*. *Crit Care Med* 2009;37:1881–5.
15 Lipowski ZJ. Delirium in the elderly patient. *N Engl J Med* 1989;320:578–82.
16 Cole MG, Ciampi A, Belzile E, *et al*. Subsyndromal delirium in older people: a systematic review of frequency, risk factors, course and outcomes. *Int J Geriatr Psychiatry* 2013;28:771–80.
17 Ouimet S, Riker R, Bergeon N, *et al*. Subsyndromal delirium in the ICU: evidence for a disease spectrum. *Intensive Care Med* 2007;33:1007–13.
18 Shim J, DePalma G, Sands LP, *et al*. Prognostic significance of postoperative Subsyndromal delirium. *Psychosomatics* 2015;56:644–51.
19 Cole M, McCusker J, Dendukuri N, *et al*. The prognostic significance of subsyndromal delirium in elderly medical inpatients. *J Am Geriatr Soc* 2003;51:754–60.
20 Levkoff SE, Liptzin B, Cleary PD, *et al*. Subsyndromal delirium. *Am J Geriatr Psychiatry* 1996;4:320–9.
21 Hakim SM, Othman AI, Naoum DO. Early treatment with risperidone for Subsyndromal delirium after on-pump cardiac surgery in the elderly. *Anesthesiology*2012;116:987–97.
22 Al-Qadheeb NS*et al*. Preventing ICU Subsyndromal delirium conversion to delirium with low-dose IV haloperidol: a double-blind, placebo-controlled pilot study. *Crit Care Med* 2016;44:583–91.
23 Besedovsky L, Lange T, Born J. Sleep and immune function. *Pflugers Arch - Eur J Physiol* 2012;463:121–37.
24 AlDabal L, Bahammam AS. Metabolic, endocrine, and immune consequences of sleep deprivation. *Open Respir Med J* 2011;5:31–43.
25 Alhola P, Polo-Kantola P. Sleep deprivation: impact on cognitive performance. *Neuropsychiatr Dis Treat* 2007;3:553–67.
26 Cedernaes J, Osorio RS, Varga AW, *et al*. Candidate mechanisms underlying the association between sleep-wake disruptions and Alzheimer's disease. *Sleep Med Rev* 2017;31:102–11.
27 Ju Y-ES, Lucey BP, Holtzman DM. Sleep and Alzheimer disease pathology—a bidirectional relationship. *Nat Rev Neurol* 2014;10:115–9.
28 Dyken ME, Afifi AK, Lin-Dyken DC. Sleep-Related problems in neurologic diseases. *Chest* 2012;141:528–44.
29 Vaz Fragoso CA, Gill TM. Sleep complaints in community-living older persons: a multifactorial geriatric syndrome. *J Am Geriatr Soc*;55:1853–66.
30 Leung JM, Sands LP, Newman S, *et al*. Preoperative sleep disruption and postoperative delirium. *J Clin Sleep Med* 2015;11:907–13.
31 Gögenur I, Bisgaard T, Burgdorf S, *et al*. Disturbances in the circadian pattern of activity and sleep after laparoscopic versus open abdominal surgery. *Surg Endosc* 2009;23:1026–31.
32 Gögenur I, Wildschiøtz G, Rosenberg J. Circadian distribution of sleep phases after major abdominal surgery. *Br J Anaesth* 2008;100:45–9.
33 Berry RBB R, Gamaldo CE, Marcus CL, *et al*. *The AASM manual for scoring of sleep and associated events: rules, terminology and technical specifications, version 2.3*. American Academy of Sleep Medicine, 2015.
34 Van Cauter E, Leproult R, Plat L. Age-Related changes in slow wave sleep and REM sleep and relationship with growth hormone and cortisol levels in healthy men. *JAMA* 2000;284:861–8.
35 Roth T, Benca RM, Erman M. An introduction to the clinical correlates of disrupted slow-wave sleep. *J Clin Psychiatry* 2010;71:e09.
36 Scullin MK. Sleep, memory, and aging: the link between slow-wave sleep and episodic memory changes from younger to older adults. *Psychol Aging* 2013;28:105–14.
37 Moote CA, Knill RL. Isoflurane anesthesia causes a transient alteration in nocturnal sleep. *Anesthesiology* 1988;69:327–31.
38 Knill RL, Moote CA, Skinner MI, *et al*. Anesthesia with abdominal surgery leads to intense REM sleep during the first post-operative week. *Anesthesiology*1990;73:52–61.
39 Orr WC, Stahl ML. Sleep disturbances after open heart surgery. *Am J Cardiol* 1977;39:196–201.
40 Johns MW, Large AA, Masterton JP, *et al*. Sleep and delirium after open heart surgery. *Br J Surg* 1974;61:377–81.
41 Ellis BW, Dudley HAF. Some aspects of sleep research in surgical stress. *J Psychosom Res* 1976;20:303–8.
42 Rosenberg-Adamsen S, Kehlet H, Dodds C, *et al*. Postoperative sleep disturbances: mechanisms and clinical implications. *Br J Anaesth* 1996;76:552–9.
43 Kavey NB, Ahshuler KZ. Sleep in herniorrhaphy patients. *Am J Surg* 1979;138:682–7.
44 Lehmkuhl P, Prass D, Pichlmayr I. General anesthesia and Postnarcotic sleep disorders. *Neuropsychobiology*1987;18:37–42.
45 Aurell J, Elmqvist D. Sleep in the surgical intensive care unit: continuous polygraphic recording of sleep in nine patients receiving postoperative care. *Br Med J* 1985;290:1029–32.
46 Rosenberg J, Wildschiodtz G, Pedersen MH, *et al*. Late postoperative nocturnal episodic hypoxaemia and associated sleep pattern. *Br J Anaesth* 1994;72:145–50.
47 Daan S, Beersma DG, Borbely AA. Timing of human sleep: recovery process gated by a circadian pacemaker. *Am J Physiol Regul Integr Comp Physiol* 1984;246:R161–83.
48 Dijk DJ, Czeisler CA. Contribution of the circadian pacemaker and the sleep homeostat to sleep propensity, sleep structure, electroencephalographic slow waves, and sleep spindle activity in humans. *J Neurosci* 1995;15:3526–38.
49 Watson PL, Pandharipande P, Gehlbach BK, *et al*. Atypical sleep in ventilated patients: empirical electroencephalography findings and the path toward revised ICU sleep scoring criteria. *Crit Care Med* 2013;41:1958–67.
50 Drouot X, Roche-Campo F, Thille AW, *et al*. A new classification for sleep analysis in critically ill patients. *Sleep Med* 2012;13:7–14.
51 Loomis AL, Harvey EN, Hobart GA. Distribution of disturbance-patterns in the human electroencephalogram, with special reference to sleep. *J Neurophysiol* 1938;1:413–30.
52 Schabus M, Hödlmoser K, Gruber G, *et al*. Sleep spindle-related activity in the human EEG and its relation to general cognitive and learning abilities. *Eur J Neurosci* 2006;23:1738–46.
53 Clawson BC, Durkin J, Aton SJ. Form and function of sleep spindles across the lifespan. *Neural Plast* 2016;2016:1–16.
54 Dempsey EW, Morison RS. The production of rhythmically recurrent cortical potentials after localized thalamic stimulation. *American Journal of Physiology-Legacy Content* 1941;135:293–300.
55 Steriade M, Deschenes M, Domich L, *et al*. Abolition of spindle oscillations in thalamic neurons disconnected from nucleus reticularis thalami. *J Neurophysiol* 1985;54:1473–97.
56 Purcell SM, Manoach DS, Demanuele C, *et al*. Characterizing sleep spindles in 11,630 individuals from the National sleep research resource. *Nat Commun* 2017;8:15930.
57 Knoblauch V, Martens WLJ, Wirz-Justice A, *et al*. Human sleep spindle characteristics after sleep deprivation. *Clinical Neurophysiology* 2003;114:2258–67.
58 Guazzelli M, Feinberg I, Aminoff M, *et al*. Sleep spindles in normal elderly: comparison with young adult patterns and relation to nocturnal awakening, cognitive function and brain atrophy. *Electroencephalogr Clin Neurophysiol* 1986;63:526–39.
59 Wei HG, Riel E, Czeisler CA, *et al*. Attenuated amplitude of circadian and sleep-dependent modulation of electroencephalographic sleep spindle characteristics in elderly human subjects. *Neurosci Lett* 1999;260:29–32.
60 Rauchs G, Schabus M, Parapatics S, *et al*. Is there a link between sleep changes and memory in Alzheimer's disease? *Neuroreport* 2008;19:1159–62.
61 Latreille V, Carrier J, Lafortune M, *et al*. Sleep spindles in Parkinson's disease may predict the development of dementia. *Neurobiol Aging* 2015;36:1083–90.
62 Allen SR, Stähelin HB, Seiler WO, *et al*. Eeg and sleep in aged hospitalized patients with senile dementia: 24-h recordings. *Experientia* 1983;39:249–55.
63 Ferrarelli F, Huber R, Peterson MJ, *et al*. Reduced sleep spindle activity in schizophrenia patients. *AJP* 2007;164:483–92.
64 Manoach DS, Pan JQ, Purcell SM, *et al*. Reduced sleep spindles in schizophrenia: a treatable endophenotype that links risk genes to impaired cognition? *Biol Psychiatry* 2016;80:599–608.
65 Chander D, García PS, MacColl JN, *et al*. Electroencephalographic variation during end maintenance and emergence from surgical anesthesia. *PLoS One* 2014;9:e106291.
66 Ferenets R, Lipping T, Suominen P, *et al*. Comparison of the properties of EEG spindles in sleep and propofol anesthesia. *Conf Proc IEEE Eng Med Biol Soc* 2006;2006:6356–9.

67 Contreras D, Destexhe A, Sejnowski TJ, *et al*. Spatiotemporal patterns of spindle oscillations in cortex and thalamus. *J Neurosci* 1997;17:1179–96.
68 Greene RW, Frank MG. Slow wave activity during sleep: functional and therapeutic implications. *Neuroscientist* 2010;16:618–33.
69 Xie L, Kang H, Xu Q, *et al*. Sleep drives metabolite clearance from the adult brain. *Science* 2013;342:373–7.
70 Tononi G, Cirelli C. Sleep and synaptic homeostasis: a hypothesis. *Brain Res Bull* 2003;62:143–50.
71 Mander BA, Marks SM, Vogel JW, *et al*. β-amyloid disrupts human NREM slow waves and related hippocampus-dependent memory consolidation. *Nat Neurosci* 2015;18:1051–7.
72 Nir Y, Staba RJ, Andrillon T, *et al*. Regional slow waves and spindles in human sleep. *Neuron* 2011;70:153–69.
73 Anaclet C, Ferrari L, Arrigoni E, *et al*. The GABAergic parafacial zone is a medullary slow wave sleep–promoting center. *Nat Neurosci* 2014;17:1217–24.
74 Landsness EC, Goldstein MR, Peterson MJ, *et al*. Antidepressant effects of selective slow wave sleep deprivation in major depression: a high-density EEG investigation. *J Psychiatr Res* 2011;45:1019–26.
75 Huber R, Felice Ghilardi M, Massimini M, *et al*. Local sleep and learning. *Nature* 2004;430:78–81.
76 Landsness EC, Crupi D, Hulse BK, *et al*. Sleep-dependent improvement in visuomotor learning: a causal role for slow waves. *Sleep* 2009;32:1273–84.
77 Marshall L, Helgadóttir H, Mölle M, *et al*. Boosting slow oscillations during sleep potentiates memory. *Nature* 2006;444:610–3.
78 Ferrara M, De Gennaro L, Bertini M. Selective slow-wave sleep (SWS) deprivation and SWS rebound: do we need a fixed SWS amount per night? *Sleep Res Online* 1999;2:15–19.
79 Dijk DJ, Beersma DGM. Effects of SWS deprivation on subsequent EEG power density and spontaneous sleep duration. *Electroencephalogr Clin Neurophysiol* 1989;72:312–20.
80 Jan Dijk D, Beersma DGM, Daan S, *et al*. Quantitative analysis of the effects of slow wave sleep deprivation during the first 3 H of sleep on subsequent EEG power density. *Eur Arch Psychiatry Neurol Sci* 1987;236:323–8.
81 Lucey BP, McCullough A, Landsness EC, *et al*. Reduced non–rapid eye movement sleep is associated with tau pathology in early Alzheimer's disease. *Sci Transl Med* 2019;11:eaau6550.
82 Mander BA, Rao V, Lu B, *et al*. Prefrontal atrophy, disrupted NREM slow waves and impaired hippocampal-dependent memory in aging. *Nat Neurosci* 2013;16:357–64.
83 Gilmore PC, Brenner RP. Correlation of EEG, computerized tomography, and clinical findings. study of 100 patients with focal delta activity. *Arch Neurol* 1981;38:371–2.
84 Gloor P, Ball G, Schaul N. Brain lesions that produce delta waves in the EEG. *Neurology* 1977;27:326–33.
85 Gloor P, KALABAY O, GIARD N. The electroencephalogram in diffuse encephalopathies: electroencephalographic correlates of grey and white matter lesions. *Brain* 1968;91:779–802.
86 Joynt RJ, Cape CA, Knott JR. Significance of focal delta activity in adult electroencephalogram. *Arch Neurol* 1965;12:631–8.
87 Walter WG, Camb MA. The location of cerebral tumours by electro-encephalography. *The Lancet* 1936;228:305–8.
88 Ginsburg DA, Pasternak EB, Gurvitch AM. Correlation analysis of delta activity generated in cerebral hypoxia. *Electroencephalogr Clin Neurophysiol* 1977;42:445–55.
89 Hanif S, Sinha S, Siddiqui KA. Electroencephalography findings in patients with acute post coronary artery bypass graft encephalopathy. *Neurosciences* 2014;19:331–3.
90 Leuchter AF, Jacobson SA. Quantitative measurement of brain electrical activity in delirium. *Int. Psychogeriatr.* 1991;3:231–47.
91 Apakama GP. *In international anesthesia research Society meeting*. San Francisco, 2016.
92 Parsons-Smith BG, Summerskill WHJ, Dawson AM, *et al*. The ELEC TROENCEPHALOGRAPH in liver disease. *Lancet* 1957;270:867–71.
93 Conn HO, Leevy CM, Vlahcevic ZR, *et al*. Comparison of lactulose and neomycin in the treatment of chronic portal-systemic encephalopathy. *Gastroenterology* 1977;72:573–83.
94 Amodio P, Marchetti P, Del Piccolo F, *et al*. Spectral versus visual EEG analysis in mild hepatic encephalopathy. *Clinical Neurophysiology* 1999;110:1334–44.
95 Van der Rijt CCD, Schalm SW, de Groot GH, *et al*. Objective measurement of hepatic encephalopathy by means of automated EEG analysis. *Electroencephalogr Clin Neurophysiol* 1984;57:423–6.
96 Young GB, Bolton CF, Austin TW, *et al*. The encephalopathy associated with septic illness. *Clin Invest Med* 1990;13:297–304.
97 Azabou E, Magalhaes E, Braconnier A, *et al*. Early standard electroencephalogram abnormalities predict mortality in septic intensive care unit patients. *PLoS One* 2015;10:e0139969.
98 Hosokawa K, Gaspard N, Su F, *et al*. Clinical neurophysiological assessment of sepsis-associated brain dysfunction: a systematic review. *Crit Care* 2014;18:674.
99 Oddo M, Taccone FS. How to monitor the brain in septic patients? *Minerva Anestesiol* 2015;81:776–88.
100 Pro JD, Wells CE. The use of the electroencephalogram in the diagnosis of delirium. *Dis Nerv Syst* 1977;38:804–8.
101 Jacobson SA, Leuchter AF, Walter DO. Conventional and quantitative EEG in the diagnosis of delirium among the elderly. *Journal of Neurology, Neurosurgery & Psychiatry* 1993;56:153–8.
102 Plaschke K, Fichtenkamm P, Schramm C, *et al*. Early postoperative delirium after open-heart cardiac surgery is associated with decreased bispectral EEG and increased cortisol and interleukin-6. *Intensive Care Med* 2010;36:2081–9.
103 Plaschke K, Hill H, Engelhardt R, *et al*. Eeg changes and serum anticholinergic activity measured in patients with delirium in the intensive care unit. *Anaesthesia* 2007;62:1217–23.
104 Jacobson SA, Leuchter AF, Walter DO, *et al*. Serial quantitative EEG among elderly subjects with delirium. *Biol Psychiatry* 1993;34:135–40.
105 Katz IR, Curyto KJ, TenHave T, *et al*. Validating the diagnosis of delirium and evaluating its association with deterioration over a one-year period. *Am J Geriatr Psychiatry* 2001;9:148–59.
106 Thomas C, Hestermann U, Kopitz J, *et al*. Serum anticholinergic activity and cerebral cholinergic dysfunction: an EEG study in frail elderly with and without delirium. *BMC Neurosci* 2008;9:86.
107 van der Kooi AW, Zaal IJ, Klijn FA, *et al*. Delirium detection using EEG: what and how to measure. *Chest* 2015;147:94–101.
108 van der Kooi AW, Leijten FSS, van der Wekken RJ, *et al*. What are the opportunities for EEG-based monitoring of delirium in the ICU? *J Neuropsychiatry Clin Neurosci* 2012;24:472–7.
109 Koponen H, Partanen J, Pääkkönen A, *et al*. Eeg spectral analysis in delirium. *J Neurol Neurosurg Psychiatry* 1989;52:980–5.
110 Ní Mhuircheartaigh R, Warnaby C, Rogers R, *et al*. Slow-Wave activity saturation and thalamocortical isolation during propofol anesthesia in humans. *Sci Transl Med* 2013;5:ra148.
111 Hughes SW, Crunelli V. Thalamic mechanisms of EEG alpha rhythms and their pathological implications. *Neuroscientist* 2005;11:357–72.
112 Berger H. Uber das Elektrenkephalogramm des Menschen: II. *Arch Psychiatr Nervenkr* 1930.
113 Gloor P. *Hans Berger on the Encephalogram of Man. Vol. Suppl 28*. Elsevier, 1969.
114 Soininen H, Reinikainen K, Partanen J, *et al*. Slowing of the dominant occipital rhythm in electroencephalogram is associated with low concentration of noradrenaline in the thalamus in patients with Alzheimer's disease. *Neurosci Lett* 1992;137:5–8.
115 Babiloni C, Lizio R, Vecchio F, *et al*. Reactivity of cortical alpha rhythms to eye opening in mild cognitive impairment and Alzheimer's disease: an EEG study. *J Alzheimers Dis* 2010;22:1047–64.
116 Dauwels J, Vialatte F, Cichocki A. Diagnosis of Alzheimer's disease from EEG signals: where are we standing? *Curr Alzheimer Res* 2010;7:487–505.
117 Dauwels J, Vialatte F, Musha T, *et al*. A comparative study of synchrony measures for the early diagnosis of Alzheimer's disease based on EEG. *Neuroimage* 2010;49:668–93.
118 Gordon EB, Sim M. The E.E.G. in presenile dementia. *J Neurol Neurosurg Psychiatry* 1967;30:285–91.
119 Liddell DW. Investigations of E.E.G. findings in presenile dementia. *J Neurol Neurosurg Psychiatry* 1958;21:173–6.
120 Prinz PN, Vitiello MV. Dominant occipital (alpha) rhythm frequency in early stage Alzheimer's disease and depression. *Electroencephalogr Clin Neurophysiol* 1989;73:427–32.
121 Brenner RP, Reynolds CF. 3rd & Ulrich, R. *F. Diagnostic efficacy of computerized spectral versus visual EEG analysis in elderly normal, demented and depressed subjects. Electroencephalogr Clin Neurophysiol* 1988;69:110–7.
122 Erkinjuntti T, Larsen T, Sulkava R, *et al*. Eeg in the differential diagnosis between Alzheimer's disease and vascular dementia. *Acta Neurol Scand* 1988;77:36–43.
123 Obrist WD, Busse EW, Eisdorfer C, *et al*. Relation of the electroencephalogram to intellectual function in senescence. *J Gerontol* 1962;17:197–206.
124 Johannesson G, Hagberg B, Gustafson L, *et al*. Eeg and cognitive impairment in presenile dementia. *Acta Neurol Scand* 1979;59:225–40.

125 Roberts MA, McGeorge AP, Caird FI. Electroencephalography and computerised tomography in vascular and non-vascular dementia in old age. *J Neurol Neurosurg Psychiatry* 1978;41:903–6.
126 Johns. M. *W. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep* 1991;14:540–5.
127 Buysse DJ, Yu L, Moul DE, *et al*. Development and validation of patient-reported outcome measures for sleep disturbance and sleep-related impairments. *Sleep* 2010;33:781–92.
128 Buysse DJ, Reynolds CF. 3rd, Monk, T. H., Berman, S. R. & Kupfer, D. J. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res* 1989;28:193–213.
129 Chung F, Abdullah HR, Liao P. Stop-Bang questionnaire: a practical approach to screen for obstructive sleep apnea. *Chest* 2016;149:631–8.
130 Yesavage JA, Sheikh JI. 9/Geriatric depression scale (GDS). *Clin Gerontol* 1986;5:165–73.
131 Nasreddine ZS, Phillips NA, Bédirian V, *et al*. The Montreal cognitive assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc* 2005;53:695–9.
132 Galvin JE, Roe CM, Powlishta KK, *et al*. The AD8: a brief informant interview to detect dementia. *Neurology* 2005;65:559–64.
133 Galvin JE, Fagan AM, Holtzman DM, *et al*. Relationship of dementia screening tests with biomarkers of Alzheimer's disease. *Brain* 2010;133:3290–300.
134 Inouye SK, van Dyck CH, Alessi CA, *et al*. Clarifying confusion: the confusion assessment method. A new method for detection of delirium. *Ann Intern Med* 1990;113:941–8.
135 Inouye SK, Westendorp RGJ, Saczynski JS. Delirium in elderly people. *Lancet* 2014;383:911–22.
136 Maybrier HR, Mickle AM, Escallier KE, *et al*. Reliability and accuracy of delirium assessments among Investigators at multiple international centres. *BMJ Open* 2018;8:e023137.
137 Wildes TS, Winter AC, Maybrier HR, *et al*. Protocol for the electroencephalography guidance of anesthesia to alleviate geriatric syndromes (engages) study: a pragmatic, randomised clinical trial. *BMJ Open* 2016;6:e011505.
138 Ely EW, Inouye SK, Bernard GR, *et al*. Delirium in mechanically ventilated patients: validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). *JAMA* 2001;286:2703–10.
139 Ely EW, Siegel MD, Inouye SK. Delirium in the intensive care unit: an under-recognized syndrome of organ dysfunction. *Semin Respir Crit Care Med* 2001;22:115–26.
140 Ely EW, Margolin R, Francis J, *et al*. Evaluation of delirium in critically ill patients: validation of the confusion assessment method for the intensive care unit (CAM-ICU). *Crit Care Med* 2001;29:1370–9.
141 Luetz A, Heymann A, Radtke FM, *et al*. Different assessment tools for intensive care unit delirium: which score to use? *Crit Care Med* 2010;38:409–18.
142 Plaschke K, von Haken R, Scholz M, *et al*. Comparison of the confusion assessment method for the intensive care unit (CAM-ICU) with the Intensive Care Delirium Screening Checklist (ICDSC) for delirium in critical care patients gives high agreement rate(s). *Intensive Care Med* 2008;34:431–6.
143 Sampson EL, West E, Fischer T. Pain and delirium: mechanisms, assessment, and management. *Eur Geriatr Med* 2020;11:45–52.
144 Vlisides PE, Thompson A, Kunkler BS, *et al*. Perioperative epidural use and risk of delirium in surgical patients: a secondary analysis of the podcast trial. *Anesth Analg* 2019;128:944–52.
145 Koyama T, Kawano T, Iwata H, *et al*. Acute postoperative pain exacerbates neuroinflammation and related delirium-like cognitive dysfunction in rats. *J Anesth* 2019;33:482–6.
146 Payen JF, Bru O, Bosson JL, *et al*. Assessing pain in critically ill sedated patients by using a behavioral pain scale. *Crit Care Med* 2001;29:2258–63.
147 Debellemaniere E, Chambon S, Pinaud C, *et al*. Performance of an ambulatory Dry-EEG device for auditory closed-loop stimulation of sleep slow oscillations in the home environment. *Front Hum Neurosci* 2018;12:88.
148 Arnal PJ, Thorey V, Debellemaniere E, *et al*. The Dreem Headband compared to polysomnography for EEG signal acquisition and sleep staging. *Sleep* 2020. doi:10.1093/sleep/zsaa097
149 Ely EW, Shintani A, Truman B, *et al*. Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. *JAMA* 2004;291:1753–62.
150 Sessler CN, Gosnell MS, Grap MJ, *et al*. The Richmond Agitation-Sedation scale: validity and reliability in adult intensive care unit patients. *Am J Respir Crit Care Med* 2002;166:1338–44.
151 Saczynski JS, Kosar CM, Xu G, *et al*. A tale of two methods: chart and interview methods for identifying delirium. *J Am Geriatr Soc* 2014;62:518–24.
152 Inouye SK, Leo-Summers L, Zhang Y, *et al*. A chart-based method for identification of delirium: validation compared with interviewer ratings using the confusion assessment method. *J Am Geriatr Soc* 2005;53:312–8.
153 Delorme A, Makeig S. EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. *J Neurosci Methods* 2004;134:9–21.
154 Mitra PP, Bokil H. *Observed brain dynamics*. 1st edn. Oxford University Press, 2008.
155 Tsanas A, Clifford GD. Stage-independent, single lead EEG sleep spindle detection using the continuous wavelet transform and local weighted smoothing. *Front Hum Neurosci* 2015;9:181.
156 Wendt SL, Christensen JAE, Kempfner J, *et al*. Validation of a novel automatic sleep spindle detector with high performance during sleep in middle aged subjects. *Annu Int Conf IEEE Eng Med Biol Soc* 2012;2012:4250–3.
157 Wamsley EJ, Tucker MA, Shinn AK, *et al*. Reduced sleep spindles and spindle coherence in schizophrenia: mechanisms of impaired memory consolidation? *Biol Psychiatry* 2012;71:154–61.
158 Martin N, Lafortune M, Godbout J, *et al*. Topography of age-related changes in sleep spindles. *Neurobiol Aging* 2013;34:468–76.
159 Mölle M, Marshall L, Gais S, *et al*. Grouping of spindle activity during slow oscillations in human non-rapid eye movement sleep. *J Neurosci* 2002;22:10941–7.
160 Bódizs R, Körmendi J, Rigó P, *et al*. The individual adjustment method of sleep spindle analysis: methodological improvements and roots in the fingerprint paradigm. *J Neurosci Methods* 2009;178:205–13.
161 Warby SC, Wendt SL, Welinder P, *et al*. Sleep-spindle detection: crowdsourcing and evaluating performance of experts, non-experts and automated methods. *Nat Methods* 2014;11:385–92.
162 Parekh A, Selesnick IW, Rapoport DM, *et al*. Detection of K-complexes and sleep spindles (DETOKS) using sparse optimization. *J Neurosci Methods* 2015;251:37–46.
163 Latta F, Leproult R, Tasali E, *et al*. Sex differences in delta and alpha EEG activities in healthy older adults. *Sleep* 2005;28:1525–34.
164 Mensen A, Riedner B, Tononi G. Optimizing detection and analysis of slow waves in sleep EEG. *J Neurosci Methods* 2016;274:1–12.
165 Inouye SK, Kosar CM, Tommet D, *et al*. The CAM-S: development and validation of a new scoring system for delirium severity in 2 cohorts. *Ann Intern Med* 2014;160:526–33.
166 Khan BA, Perkins AJ, Gao S, *et al*. The confusion assessment method for the ICU-7 delirium severity scale: a novel delirium severity instrument for use in the ICU. *Crit Care Med* 2017;45:851–7.
167 Landolt HP, Dijk DJ, Achermann P, *et al*. Effect of age on the sleep EEG: slow-wave activity and spindle frequency activity in young and middle-aged men. *Brain Res* 1996;738:205–12.
168 Nicolas A, Petit D, Rompré S, *et al*. Sleep spindle characteristics in healthy subjects of different age groups. *Clin Neurophysiol* 2001;112:521–7.
169 Crowley K, Trinder J, Kim Y, *et al*. The effects of normal aging on sleep spindle and K-complex production. *Clin Neurophysiol* 2002;113:1615–22.
170 Carrier J, Land S, Buysse DJ, *et al*. The effects of age and gender on sleep EEG power spectral density in the middle years of life (ages 20-60 years old). *Psychophysiology* 2001;38:232–42.
171 Derbyshire AJ, Rempel B, Forbes A, *et al*. The effects of anesthetics on action potentials in the cerebral cortex of the cat. *Am J Physiol* 1936;116:577–96.
172 Shortal BP, Hickman LB, Mak-McCully RA, *et al*. Duration of EEG suppression does not predict recovery time or degree of cognitive impairment after general anaesthesia in human volunteers. *Br J Anaesth* 2019;123:206–18.
173 Wildes TS, Mickle AM, Ben Abdallah A, *et al*. Effect of Electroencephalography-Guided anesthetic administration on postoperative delirium among older adults undergoing major surgery: the engages randomized clinical trial. *JAMA* 2019;321:473–83.
174 Cohen J. *Statistical Power Analysis for the Behavioral Sciences*. Lawrence Erlbaum Associates, 1988.
175 Lachman ME, Agrigoroaei S, Tun PA, *et al*. Monitoring cognitive functioning: psychometric properties of the brief test of adult cognition by telephone. *Assessment* 2014;21:404–17.
176 Tun PA, Lachman ME. Telephone assessment of cognitive function in adulthood: the brief test of adult cognition by telephone. *Age Ageing* 2006;35:629–32.

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	Yes (available on trial registry NCT 03291626)
Protocol version	3	Date and version identifier	N/A
Funding	4	Sources and types of financial, material, and other support	22
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 22
	5b	Name and contact information for the trial sponsor	22
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	N/A

	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	N/A
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3-4
	6b	Explanation for choice of comparators	5-7
Objectives	7	Specific objectives or hypotheses	7-8
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	9
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	10
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	9-10
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10-13
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	13
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	13-14
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A

Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	10-14
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	12-13, Figure 3
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	18-19
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	10
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	N/A
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	N/A
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	N/A
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	10-14
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	12-13
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	Supplementary File 2
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	15-18
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	19-20
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	18
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	22
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	Supplementary File 2
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	22
Ethics and dissemination			

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	23
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	21-22
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	10
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	Supplementary File 2
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	23
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	23
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	Supplementary File 2
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	21
	31b	Authorship eligibility guidelines and any intended use of professional writers	23
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	23-24
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplementary File 2

Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.

Washington University in St.Louis

INFORMED CONSENT DOCUMENT

Project Title: P-DROWS-E / Prognosticating Delirium Recovery Outcomes Using Wakefulness and Sleep Electroencephalography

Principal Investigator: Ben J.A. Palanca, MD, PhD, MSc

Research Team Contact: Thomas Nguyen, Nguyen.t@wustl.edu, 314-273-2454

This consent form describes the research study and helps you decide if you want to participate. It provides important information about what you will be asked to do during the study, about the risks and benefits of the study, and about your rights and responsibilities as a research participant. By signing this form, you are agreeing to participate in this study.

- You should read and understand the information in this document including the procedures, risks and potential benefits.
- If you have questions about anything in this form, you should ask the research team for more information before you agree to participate.
- You may also wish to talk to your family or friends about your participation in this study.
- Do not agree to participate in this study unless the research team has answered your questions and you decide that you want to be part of this study.

WHAT IS THE PURPOSE OF THIS STUDY?

This is a research study. We invite you to participate in this research study because you are going to undergo a cardiac surgical procedure. We want to understand your sleep and brain function before, during, and after surgery.

Postoperative delirium is a condition in which patients develop temporary difficulties in maintaining attention and thinking clearly. These new problems can appear after surgery and change throughout the day. This confusion can last several days.

The overall purpose of this study is to measure brain activity during sleep and wakefulness to learn about their relationships to delirium after surgery. While you may not feel like your normal self during the study, you are in the best position to help us learn how to improve the recovery of brain function and sleep in others having surgery. We need to learn from those who have and have not become confused after their surgical procedure.

WHAT WILL HAPPEN DURING THIS STUDY?

Your participation in this study involves the study of your brain activity at three periods: (1) 1-2 days within the weeks before you undergo surgery, (2) during surgery, and (3) for up to 7 days after you have had surgery. We may also contact you after hospital discharge to study your thinking abilities. This research study will take place at home and at the Washington University School of Medicine campus.

Recording Before Surgery: The research team will show you how to wear a lightweight headband for the study. This device, the DREEM is used to assess sleep quality at home. It will allow us to record brain electrical activity from your scalp, using electroencephalography, or EEG. EEG is currently used to study brain function in the operating room and for assisting in the diagnosis of sleep problems.

Washington University in St. Louis

First, we will show you the DREEM, and how to wear it. After we show you an instruction card, we will determine the best fit for wearing the device. We will then have you wear the DREEM so that we may obtain baseline data. We will then ask you to stay awake with your eyes closed and open. We may ask you to do some simple tasks, such as wiggling your toes or tapping your fingers. The research team will also ask you some questions about any pain you are experiencing and how you are thinking and feeling. You will also be asked to complete a short cognitive assessment and fill out surveys regarding your quality of sleep and sleep habits, how sleepy you feel during various activities, your mood, and some basic demographic information. We will then send you home with the DREEM to wear while you sleep for 1-2 nights before you have surgery. We will call you before and after every day of recording to assist you in this process.

We will ask you to bring the DREEM back on the day of surgery. Alternatively, if you are in the hospital on the night before surgery, we will help you wear it and discuss with your nurses and doctors how it will not impede their care for you.

Alternate Operations Due to COVID-19: The research team will send a lightweight headband to your home. We will email or text you a link to an instructional video to show you how to use the device and a link to complete our surveys electronically. Before going to sleep, you will be asked to stay awake with your eyes open for 4 minutes followed by eyes closed for 4 minutes while wearing the headband. We will contact you before and after each day of recording to assist you in this process. Depending on your convenience, we will ask you to bring the DREEM back on the day of surgery or ship the device back to us using a prepaid shipping package.

Recording During Surgery: Before you go into surgery, a member of the research team will help you wear the DREEM. We may ask you to remain awake with your eyes open and closed for a few minutes before you wear it throughout your surgery. We will be in contact with your nurses and physicians to ensure that the device will not interfere with your care.

Alternate Operations Due to COVID-19: On the day of surgery, we may also you to complete a short cognitive assessment before surgery due to limited in-person interaction at baseline.

Recording After Surgery: After your surgery is completed, the research team will check on the device and have you continue wearing the DREEM throughout the day and night. This will continue up to the first seven days after surgery. The team will ask you more questions about any pain you are experiencing and how you are thinking and feeling. We will again ask you to do simple tasks or to otherwise lay still with your eyes closed. Our interaction with you on these days will mainly be around 7 AM, 1 PM, and 7 PM, and should take roughly 10-30 minutes. At this time, we can also adjust the device to improve your comfort if needed.

Outpatient Follow-Up: After you have left the hospital, we may contact you at certain time points to assess your thinking. This will be performed by phone or in the hospital. We would do our best to coordinate with your clinical follow-up appointments. During these 15-20 minute follow-ups, we will ask you to answer a series of questions. We will audio-record these interactions to better interpret your responses. If the follow-up is in person, you may be asked to wear the DREEM device during the session.

At the above time points and after the study, we will want to check on your satisfaction and determine

Washington University in St.Louis

ways to improve comfort and tolerability, to aid future patients in the study. Additionally, we may continually monitor your electronic medical record during your enrollment to help coordinate timing of study procedures. We will also collect information from your electronic medical record pertaining to your surgery, recovery progress, and indicators of mental status including delirium. We would continue accessing these data after you have been discharged from the hospital.

Will you save my samples or research data to use in future research studies?

As part of this study, we are obtaining cognitive assessments and EEG data from you. We would like to use these data for studies going on right now as well as studies that are conducted in the future. These studies may provide additional information that will be helpful in understanding brain recovery after surgery or other diseases or conditions, including research to develop investigational tests, treatments, drugs or devices that are not yet approved by the U.S. Food and Drug Administration. It is unlikely that what we learn from these studies will have a direct benefit to you. There are no plans to provide financial compensation to you should this occur. By allowing us to use your EEG data, you give up any property rights you may have in the EEG data.

We will share your data with other researchers. These researchers may be at Washington University, at other research centers and institutions, or industry sponsors of research. We may also share your research data with large data repositories (a repository is a database of information) for broad sharing with the research community. If your individual research data is placed in one of these repositories only qualified researchers, who have received prior approval from individuals that monitor the use of the data, will be able to look at your information.

Your data will be stored without your name or any other kind of link that would enable us to identify which sample(s) or data are yours. Therefore, it will be available for use in future research studies indefinitely and cannot be removed.

Video Recording/Photographs/Audio Recording

Part of the study involves videotaping and/or photographing the DREEM headband while it is on your head. Video clips and/or photographs of our recording sessions will be used to gauge your brain state, allow for prompt intervention in the case of any safety concerns, and for demonstration purposes for potential participants.

We will also use the photographs and/or video clippings in future abstract/manuscript submissions or academic conferences. It is customary to include photographs or video clips when presenting findings using new brain monitoring technologies. No identifiers or personal health information will be associated with the photographic or video materials used in publications, beyond the images. Reasonable efforts will be made to conceal your identity if the pictures or images are used. Your eyes will be covered in photographs to hide your identity.

Video will be stored electronically with an assigned code instead of your name and will be accessible only to the research staff on this project. Videos and photos used for education will be kept for 7 years. For academic presentations, we will keep the videos/photos indefinitely. Alternatively, they may be destroyed upon the participant's written request.

Additionally, audio recordings may be requested for the cognitive task performance portion of the study. These recordings will only contain responses to task items and no identifying information aside from

Washington University in St.Louis

coded subject identifiers. These recordings will be used to further evaluate and verify your cognitive performance during certain tasks.

I give you permission to make video recordings/photographs/audio recordings of me during this study.

_____ Yes **_____ No**
Initials **Initials**

HOW MANY PEOPLE WILL PARTICIPATE?
Approximately 220 people will take part in this study conducted by investigators at Washington University.

HOW LONG WILL I BE IN THIS STUDY?
Your direct participation in the study will take up to 10 days, with one – two days of recording before surgery and seven days of recording during and after surgery. We will contact you within a week after your enrollment in the study in person or by telephone to obtain feedback from your experience in the study. We would like to determine whether you had any problems during your involvement. We will also maintain phone contact in the months after your inpatient stay to coordinate and collect data on your thinking abilities.

WHAT ARE THE RISKS OF THIS STUDY?
You may experience one or more of the risks indicated below from being in this study. In addition to these, there may be other unknown risks, or risks that we did not anticipate, associated with being in this study.

DREEM EEG [Electroencephalography]: Skin irritation may occur from wearing these electrodes. Some discomfort may occur when we change the electrodes, particularly those over your hair.

Questionnaires: There are no risks associated with the questionnaires.

Breach of Confidentiality: One risk of participating in this study is that confidential information about you may be accidentally disclosed. We will use our best efforts to keep the information about you secure. Please see the section in this consent form titled "How will you keep my information confidential?" for more information.

WHAT ARE THE BENEFITS OF THIS STUDY?
You will not benefit from being in this study. However, we hope that, in the future, other people might benefit from this study because the results may increase our understanding of the changes in brain function after surgery.

WILL IT COST ME ANYTHING TO BE IN THIS STUDY?
You will not have any costs for being in this research study.

You and/or your medical/hospital insurance provider will remain responsible for your regular medical care expenses.

Smith SK, *et al. BMJ Open* 2020; 10:e044295. doi: 10.1136/bmjopen-2020-044295

Washington University in St. Louis

WILL I BE PAID FOR PARTICIPATING?

You will be paid for being in this research study. You will need to provide your social security number (SSN) in order for us to pay you. You may choose to participate without being paid if you do not wish to provide your social security number (SSN) for this purpose. You may also need to provide your address if a check will be mailed to you. If your social security number is obtained for payment purposes only, it will not be retained for research purposes.

You will be compensated a maximum of $300 for study involvement, depending on when you enter the study in relation to your surgery. You will receive $50 for each preoperative (before surgery) recording (up to $100 total for two days) for helping us record data while you sleep at home and for bringing the device back to us. You will receive $25 for each postoperative study day, including the day of surgery and up to seven days after surgery (maximum $200 for eight days). Cab fare will be arranged and paid for ahead of any study-related outpatient visits by study staff to cover the cost of transportation for study procedures. If otherwise requested by the patient, parking vouchers will also be assigned to participants to cover the cost of parking for the duration of any required study-related visits.

WHO IS FUNDING THIS STUDY?

The National Institutes of Health (NIH) is funding this research study. This means that Washington University is receiving payments from NIH to support the activities that are required to conduct the study. No one on the research team will receive a direct payment or increase in salary from NIH for conducting this study.

WHAT IF I AM INJURED AS A RESULT OF THIS STUDY?

Washington University investigators and staff will try to reduce, control, and treat any complications from this research. If you feel you are injured because of the study, please contact the investigator (314)-362-7823) and/or the Washington University Human Research Protection Office at 1-(800)-438-0445.

Decisions about payment for medical treatment for injuries relating to your participation in research will be made by Washington University. If you need to seek medical care for a research-related injury, please notify the investigator as soon as possible.

HOW WILL YOU KEEP MY INFORMATION CONFIDENTIAL?

We will keep your participation in this research study confidential to the extent permitted by law. However, it is possible that other people such as those indicated below may become aware of your participation in this study and may inspect and copy records pertaining to this research. Some of these records could contain information that personally identifies you.

- Government representatives, (including the Office for Human Research Protections) to complete federal or state responsibilities
- The U.S. Food and Drug Administration
- The National Institutes of Health
- Hospital or University representatives, to complete Hospital or University responsibilities
- Information about your participation in this study may be documented in your health care records and be available to your health care providers who are not part of the research team.
- The last four digits of your social security number may be used in hospital or University systems to track billing information for research procedures
- Washington University's Institutional Review Board (a committee that oversees the conduct of

Washington University in St.Louis

research involving human participants) and the Human Research Protection Office. The Institutional Review Board has reviewed and approved this study.

To help protect your confidentiality, we will have all paper documents locked in a filing cabinet in a locked office of a member of the study team. We will keep all electronic documents on secured servers that are password protected and have various state of the art firewall protections with frequent upgrades of these protections. Access to these electronic research files will be restricted to members of the research team and will be controlled by the principal investigator. If we write a report or article about this study or share the study data set with others, we will do so in such a way that you cannot be directly identified.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.
To further protect your privacy, this research is covered by a Certificate of Confidentiality from the federal government. This means that the researchers can refuse to disclose information that may identify you in any legal or court proceeding or to anyone who is not connected with the research except if:

- there is a law that requires disclosure, such as to report child abuse and neglect, or harm to self or others*;*
- you give permission to disclose your information, including as described in this consent form; or
- it is used for other scientific research allowed by federal law.

You have the right to share your information or involvement in this study with anyone at any time. You may also give the research team permission to disclose your information to a third party or any other person not connected with the research.

If information about you or your involvement in this research is placed in your medical record the information may no longer be protected under the Certificate. However, information in your medical records is protected in other ways.

Are there additional protections for my health information?

Protected Health Information (PHI) is health information that identifies you. PHI is protected by federal law under HIPAA (the Health Insurance Portability and Accountability Act). To take part in this research, you must give the research team permission to use and disclose (share) your PHI for the study as explained in this consent form. The research team will follow state and federal laws and may share your health information with the agencies and people listed under the previous section titled, "How will you keep my information confidential?"

Once your health information is shared with someone outside of the research team, it may no longer be protected by HIPAA.

The research team will only use and share your information as talked about in this form or as permitted or required by law. When possible, the research team will make sure information cannot be linked to you (de-identified). Once information is de-identified, it may be used and shared for other purposes not discussed in this consent form. If you have questions or concerns about your privacy and the use of your PHI, please contact the University's Privacy Officer at 866-747-4975.

Washington University in St.Louis

Although you will not be allowed to see the study information, you may be given access to your health care records by contacting your health care provider.

If you decide not to sign this form, it will not affect

- your treatment or the care given by your health provider.
- your insurance payment or enrollment in any health plans.
- any benefits to which you are entitled.

However, it will not be possible for you to take part in the study.

If you sign this form:

- You authorize the use of your PHI for this research
- This authorization does not expire.
- You may later change your mind and not let the research team use or share your information (you may revoke your authorization).
    - To revoke your authorization, complete the withdrawal letter, found in the Participant section of the Human Research Protection Office website at https://hrpo.wustl.edu/participants/withdrawing-from-a-study/ or you may request that the investigator send you a copy of the letter.
        - **If you revoke your authorization:**
            - The research team may only use and share information already collected for the study.
            - Your information may still be used and shared as necessary to maintain the integrity of the research, for example, to account for a participant's withdrawal from the research study or for safety reasons.
            - You will not be allowed to continue to participate in the study.

Can we contact you by email?

We would like to contact you by email for the purposes listed below. Some of these emails may contain health information that identifies you.

- Provide you with a copy of the informed consent, links to instructional contents, links to survey questionnaires, and scheduling.

Only the research team will have access to your email communications. We will only communicate by email to send you the information listed above. If you have any questions or need to contact us for an urgent or emergent situation, please contact the research team member identified at the top of this document.

You should be aware that there are risk associated with sending your health information via email.

- There is always a risk that the message could be intercepted or sent to the wrong email address. To avoid sending messages to the wrong email address, the first email we send you will be a test message to ensure we have the correct email address.
- When using any computer, you should be careful to protect your username and password. Make sure you log-out before getting up from the computer.
- If you share a home computer with other family members, and do not want them to know you are participating in this study make sure you provide an email address that only you can access.

Washington University in St.Louis

- Your employer will have access to any email communications sent or received on any electronic devices used for work or through a work server.

Do you agree to allow us to send your health information via email?

_____ Yes **_____ No**
Initials **Initials**

IS BEING IN THIS STUDY VOLUNTARY?
Taking part in this research study is completely voluntary. You may choose not to take part at all. If you decide to be in this study, you may stop participating at any time. Any data that was collected as part of your participation in the study will remain as part of the study records and cannot be removed.

If you decide not to be in this study, or if you stop participating at any time, you won't be penalized or lose any benefits for which you otherwise qualify.

What if I decide to withdraw from the study?
You may withdraw by telling the study team you are no longer interested in participating in the study or you may send in a withdrawal letter. A sample withdrawal letter can be found at https://hrpo.wustl.edu/participants/withdrawing-from-a-study/ under Withdrawing from a Research Study.

Will I receive new information about the study while participating?
If we obtain any new information during this study that might affect your willingness to continue participating in the study, we'll promptly provide you with that information.

Can someone else end my participation in this study?
Under certain circumstances, the Principal Investigator (PI) might decide to end your participation in this research study earlier than planned. This might happen for no reason or because you are found to be ineligible for the study, or because your involvement causes significant distress/discomfort.

WHAT IF I HAVE QUESTIONS?
We encourage you to ask questions. If you have any questions about the research study itself, please contact: We encourage you to ask questions. If you have any questions about the research study itself, please contact:

Principal Investigator: Ben Palanca, M.D., Ph.D., M.Sc.
Mailing Address: Washington University School of Medicine / Department of Anesthesiology / Campus Box 8054 / 660 South Euclid Avenue / St. Louis, MO / 63110
Telephone: 314-273-9076.

If you have questions, concerns, or complaints about your rights as a research participant, please contact the Human Research Protection Office at 660 South Euclid Avenue, Campus Box 8089, St. Louis, MO 63110, 1-(800)-438-0445, or email hrpo@wustl.edu. General information about being a research participant can be found on the Human Research Protection Office web site, http://hrpo.wustl.edu. To offer input about your experiences as a research participant or to speak to someone other than the research staff, call the Human Research Protection Office at the number above.

Washington University in St.Louis

This consent form is not a contract. It is a written explanation of what will happen during the study if you decide to participate. You are not waiving any legal rights by agreeing to participate in this study. As a participant you have rights and responsibilities as described in this document and including:

- To be given enough time before signing below to weigh the risks and potential benefits and decide if you want to participate without any pressure from the research team or others.
- To understand all of the information included in the document, have your questions answered, and receive an explanation of anything you do not understand.
- To follow the procedures described in this document and the instructions of the research team to the best of your ability unless you choose to stop your participation in the research study.
- To give the research team accurate and complete information.
- To tell the research team promptly about any problems you have related to your participation, or if you are unable to continue and wish to stop participating in the research study.

Your signature indicates that this research study has been explained to you, that your questions have been answered, and that you agree to take part in this study. You will receive a signed and dated copy of this form.

Do not sign this form if today's date is after EXPIRATION DATE: 02/05/21.

_____ _____
(Signature of Participant) (Date)

_____
(Participant's name – printed)

Statement of Person Who Obtained Consent

The information in this document has been discussed with the participant or, where appropriate, with the participant's legally authorized representative. The participant has indicated that he or she understands the risks, benefits, and procedures involved with participation in this research study.

_____ _____
(Signature of Person who Obtained Consent) (Date)

_____
(Name of Person who Obtained Consent - printed)