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EEG - Guided Anesthetic Care and Postoperative Delirium
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Impact of electroencephalogram – guided anesthetic care on delirium after laparoscopic surgery: *a randomized controlled trial*

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Section A: Study Protocol

Study Intervention:
Electroencephalogram – guided anesthetic care using SedLine Brain Function Monitoring

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Contents

1. Background

Delirium is an acute brain dysfunction characterized by inattention, disorganized thinking, and a fluctuating course. Delirium is a common complication after surgery, with an incidence up to 70%, depending on patient's age and type of surgery [1]. Patients who experience postoperative delirium is associated with a longer ICU stay, prolonged mechanical ventilation, increased hospital length of stay and health care cost. They also are at increased risk for institutionalization, death, and dementia after hospital discharge. Delirium prevention is expected to reduce morbidity, mortality, hospital length of stay (LOS) and cost, as well as improve the quality of life.

Multiple modifiable and unmodifiable risk factors have been recognized, such as age, type of surgery, ICU admission, pain, and certain medications. Age is a typical example of unmodifiable risk factor. The modifiable risk factors are the targets of delirium prevention. One of the modifiable risk factors is the dosing of sedative or anesthetic agents. Certain features of the intraoperative electroencephalogram (EEG) have been associated with postoperative delirium [2-5]. It was shown that patients with increased low-frequency EEG activity during the rewarming phase of cardiac surgery are at increased risk for postoperative complications, including delirium [2]. EEG burst suppression (BS) is associated with increased incidences of postcoma delirium in ICU patients [3] and postoperative delirium in surgical patients being admitted to ICU after surgery [4].

The advancement of technology allows non-invasive, continuous and convenient EEG monitoring with the adhesive probe placed on patient's forehead. However, the monitor itself is not the goal because pure monitoring without meaningful and effective intervention does not change the outcome. A monitor is valuable only if effective interventions guided by this monitor exist and these interventions improve patient outcome. This principle applies in the clinical use of EEG monitoring. The previous randomized controlled trials investigating the effect of processed EEG – guided anesthetic care on postoperative delirium after general anesthesia was based on the derived number (0-100) provided by BIS monitor. The incidence and duration of EEG burst suppression was not characterized in these studies [6-8]. The characteristic of EEG frequencies, i.e. delta, theta, alpha, and beta, was not reported. In addition, the incidence and character of post-anesthesia care unit (PACU) delirium was not investigated. However, PACU delirium have a strong association with postoperative delirium [9-11].

SedLine® (Masimo, CA) Brain Function Monitoring is an FDA-approved non-invasive EEG monitoring technology. SedLine is different from BIS in many regards. It simultaneously displays four channels of frontal, bilateral EEG waveforms. The Patient State Index (PSI) is a processed EEG parameter that is related to the effect of anesthetic agents (i.e. the popular numeric depth concept). The Density Spectral Array (DSA) provides left and right spectrograms representing the power of the EEG across the frequency range on both sides of the brain. It also provides the burst suppression information (%) and the real-time spectral edge EEG frequency. These parameters are meant to be used in clinical practice to guide anesthesia management.

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4) Fritz BA, Kalarickal PL, Maybrier HR, Muench MR, Dearth D, Chen Y, Escallier KE, Ben Abdallah A, Lin N, Avidan MS. Intraoperative Electroencephalogram Suppression Predicts Postoperative Delirium. Anesth Analg. 2016;122(1):234-42.
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8) Chan MT, Cheng BC, Lee TM, Gin T; CODA Trial Group. BIS-guided anesthesia decreases postoperative delirium and cognitive decline. J Neurosurg Anesthesiol. 2013;25(1):33-42.
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11) Sharma PT, Sieber FE, Zakriya KJ, Pauldine RW, Gerold KB, Hang J, Smith TH. Recovery room delirium predicts postoperative delirium after hip-fracture repair. Anesth Analg. 2005;101(4):1215-20.

2. Purpose of the study

To investigate the impact of the anesthetic care guided by EEG monitor (SedLine) on (1) the incidence of delirium in post-anesthesia care unit (PACU) and within the first five days after laparoscopic surgery and (2) the incidence of in-hospital complications and 30-day mortality in adult patients after laparoscopic surgery.

3. Recruitment of subjects

Potential participants will be identified within 7 days before the scheduled surgery by the research team.

3.1 Inclusion criteria

1) Age ≥ 50 years;
2) ASA Physical Score I-III
3) Scheduled to undergo an elective laparoscopic intra-abdominal surgery under general anesthesia with endotracheal intubation;
4) Extubation expected after surgery;
5) Scheduled to stay in hospital for > 3 days after surgery.

3.2 Exclusion criteria

Patients will be excluded if they meet any of the following criteria.

1) Refuse to participate;
2) Emergent surgery;
3) Trauma surgery;
4) Preoperative history of stroke, schizophrenia, major depression, Parkinson's disease, epilepsy, or dementia;
5) Inability to communicate in the preoperative period due to illiteracy, language difficulties, or significant hearing or visual impairment;
6) Inability to complete MMSE and delirium survey;
7) Severe cardiac disease including low-output cardiac failure defined as a preoperative left ventricular ejection fraction < 30%, or arrhythmia with pacemaker or AICD placement;
8) Severe hepatic dysfunction being evaluated for liver transplantation or with a Child-Pugh Class C classification;
9) Severe renal dysfunction requiring renal replacement therapy before surgery;
10) Those with preoperative ASA classification of 4 or who are unlikely to survive for more than 5 days after surgery.

3.3 Criteria of drop out

1) Withdrawal of consent by the participants themselves;
2) Procedure converted to open surgery (patients will be followed for intention-to-treat analysis);
3) Loss of follow-up (patients may be excluded from per-protocol analysis);
4) Ordered to exit by the investigators or attending physicians (occurrence of severe complications or adverse events);
5) Cases of unmasked blindness (patients will be excluded from per-protocol analysis);
6) Patients who remain intubated after surgery (patients will be excluded from per-protocol analysis).

For drop out cases, the detailed reasons will be recorded and the therapeutic effects recorded in the previous encounter will be regarded as the final results. The Case Report Forms (CRFs) of these cases will be preserved for future reference.

3.4 Criteria of Rejection

Enrolled cases who meet any of the following criteria will be excluded from further per-protocol analysis.

1) Intervention protocol is not executed;
2) No or incomplete study record;

Enrolled cases who meet any of the following criteria will be excluded from further as-treated analysis.

Unable to evaluate the effectiveness of intervention (e.g., missing SedLine data).

For rejected cases, the detailed reasons will be recorded and CRFs will be preserved for reference. The results of these cases will be excluded in analysis of therapeutic effects.

3.5 Criteria of Study Interruption

Study will be interrupted in the following situations:

1) Severe safety issues occurred during the study;
2) Serious mistakes found in the protocol;
3) Fund or management problem of the investigators;
4) Study terminated by the administrative authority.

Study interruption may be transient or permanent. All recorded CRFs will be preserved for reference in case of study interruption.

4. Study design

4.1 Type of the study

The study is a prospective, double blinded, randomized and controlled parallel trial. (The only people who know the patient's assignment are the study coordinator and the anesthesia team who takes care of the patient during surgery.)

4.2 Sample size calculation

The incidence of postoperative delirium is about 14% in in elderly patients who underwent laparoscopic surgery for colorectal cancer [Tei et al., 2016]. We assume that the incidence of postoperative delirium will be reduced by 1/3 in patients receiving EEG-guided care [Chan et al., 2013]. With a two-sided significance and power set at 0.05 and 80%, respectively, the sample size required to detect the reduction is 742 patients per group. Taking into account a loss-to-follow-up rate of about 5%, we plan to enroll 780 patients in each group.

1) Tei M, Wakasugi M, Kishi K, Tanemura M, Akamatsu H. Incidence and risk factors of postoperative delirium in elderly patients who underwent laparoscopic surgery for colorectal cancer. Int J Colorectal Dis. 2016 Jan;31(1):67-73.

2) Chan MT, Cheng BC, Lee TM, Gin T; CODA Trial Group. BIS-guided anesthesia decreases postoperative delirium and cognitive decline. J Neurosurg Anesthesiol. 2013;25(1):33-42.

5. Randomization and blinding

5.1 Randomization

1) A biostatistician who does not participate in data management and statistical analysis will generate random numbers in a 1:1 ratio;
2) The results of randomization will be sealed in sequentially numbered envelops, stored at the site of investigation, and managed by the study coordinator.
3) Timing of randomization of individual patient: 30-60 mins before surgery

5.2 Blinding

1) A study coordinator will be assigned to distribute the EEG monitor, open the randomization envelope, inform the anesthesiologist of the patient's assignment, enforce the execution of the study protocol, collect the data during surgery, and coordinate the overall research effort;
2) For each recruited patient, the anesthesiologist is one of the two persons who know the patient assignment. The other person is the study coordinator who opens the randomization envelope. The anesthesiologist will be instructed of how to use the EEG monitor to guide the anesthesia care per research protocol if the patient is assigned to the intervention arm;
3) For each recruited patient, the study coordinator is the only research team member who comes to the Operating Room to monitor the execution of the study protocol;
4) Two research personnel, different to the study coordinator, will be responsible for postoperative follow-up including delirium assessment starting at the post-anesthesia care unit. These two personnel are blinded to patient randomization;
5) The anesthesiologist who executes the study protocol and the research personnel who collects postoperative outcome data do not share any information related to patient assignment;
6) Statistical analysis will be performed independently by the designated statistician at Yale University.

6. Intervention protocol

6.1 Monitor used in the intervention group

1) Name: SedLine Brain Function Monitoring;
2) Product specification: FDA-approved non-invasive EEG monitor;
3) Manufacturer: Masimo Corporation, Irvine, CA.

6.2 Monitor used in the control group

1) Name: SedLine Brain Function Monitoring;

2) Product specification: FDA-approved non-invasive EEG monitor;
3) Manufacturer: Masimo Corporation, Irvine, CA.

6.3 Monitoring

1) All recruited patients from either control or intervention group will receive SedLine EEG monitoring;
2) A study coordinator will distribute the monitor 30 mins before the arrival of the patient in the Operating Room;
3) The probe of SedLine monitor will be placed on patient's forehead after the patient's arrival in the Operating Room and before the anesthesia induction;
4) The monitor data will be collected by the study coordinator.

6.4 Anesthetic care guided by EEG monitoring

1) The monitor screen in the control arm is covered and blinded to the anesthesiologist;
2) The monitor in the intervention arm is used by the anesthesiologist to adjust the anesthetic care.
3) The goal in the intervention arm is to maintain SEF 10-15 throughout surgery. Avoid burst-suppression.
4) In the intervention arm, the anesthesia induction is achieved via propofol pump infusion (slow and controlled). The goal is to avoid burst-suppression and maintain SEF > 10 throughout anesthesia induction.
5) The anesthesia maintenance is achieved via the protocol detailed below (6.5). The SedLine-guided intervention protocol is detailed in the **Supplemental remark 1. SedLine-Guided Intervention Flow Chart**.

6.5 Anesthesia protocol for both intervention and control group

1) During the study period (from preop to postop day 5), anticholinergics such as scopolamine are strictly prohibited; atropine or glycopyrrolate can only be used for treatment of bradycardia; the use of midazolam for anxiolysis is allowed but not encouraged;
2) In both arms, the anesthesia induction is per standard care using agents of lidocaine, propofol, sufentanyl and muscle relaxant. The administration of propofol in the intervention arm is via pump infusion and guided by SedLine.
3) The anesthesia is maintained using propofol infusion (0-200 mcg/kg/min) and remifentanil infusion (0.05-0.2 mcg/min/kg). Sufentanyl and muscle relaxant boluses can be used during surgery.
4) The anesthetic adjustment in the control arm is per the conventional practice (EEG monitored but blinded to anesthesia team) and in the intervention arm per the **Supplemental remark 1. SedLine-Guided Intervention Flow Chart**.

7. Data collection

7.1 Preoperative data

1) Determine patient's eligibility based on the inclusion and exclusion criteria;
2) Mini-mental Status Exam;
3) Demographic data, past medical and surgical history, medications taken at home and in hospital;
4) Electrocardiogram, echocardiogram if available;
5) Lab results.

7.2 Intraoperative data

1) Surgical details including type and time of surgery;
2) Anesthetic details including the name and dose of any drugs used during surgery;
3) The total dose of propofol used for anesthesia induction and maintenance;
4) Inputs and outputs including the name and volume of the fluid being administered, the estimated blood loss, the urine output, and any blood products being transfused;
5) EEG data including the occurrence, duration and percentage of burst-suppression, SEF and PSI (specific to SedLine monitor).

7.3 Postoperative data

1) PACU Delirium: Occurrence of delirium in PACU will be assessed using the CAM-ICU 30 mins after extubation and before PACU discharge.
2) Postoperative Delirium (POD): POD will be assessed twice daily (8:00-10:00 am, and 18:00-20:00 pm) for 5 days from postoperative day 1 to 5 or until the patient is discharged home if the patient stays in hospital < 5 days. CAM is used for delirium assessment if the patient is on the floor; otherwise, CAM-ICU is used if the patient is in the ICU. Investigators for POD assessment will be trained by a psychiatrist to use CAM and CAM-ICU before the trial is commenced.
3) Non-delirium Complications: Any complications occurred within the first 30 days after surgery (for example: cardiac events, cerebrovascular events, renal injury, GI complications, infections, etc.) will be documented. Patients will be assessed via phone call if they are discharged before day 30 after surgery.
4) Subjective Pain Score: It will be assessed at PACU and 24 hours after surgery using the Numeric Rating Scale (NRS) (an 11-point scale where 0 indicates no pain and 10 indicates the worst pain).
5) Subjective Sleep Quality: It will be assessed at 8:00 am during the first postoperative day using the NRS (an 11-point scale where 0 indicates the best possible sleep and 10 indicates the worst possible sleep).
6) Length of Hospital Stay: The readiness for discharge will be used as the last day of hospitalization.
7) All-cause 30-day Mortality: Patients or family members will be called for assessment.
8) Adverse Events: If an adverse event occurs during patient hospitalization, it will be followed up until its disappearance or therapy ends.

8. Outcome

8.1 Primary outcome

Incidence of postoperative delirium during the first 5 days after surgery.

8.2 Secondary outcomes

The secondary outcomes are as follows:

1) Incidence of emergence delirium;
2) Composite complication classified as Clavien-Dindo grade II or greater within postoperative 30 days;
3) 24-hour postoperative nausea and vomiting (PONV);
4) MMSE score change;
5) Length of hospital stay;
6) Intensive care unit (ICU) admission;
7) 30-day hospital readmission;
8) 30-day all-cause mortality

Postoperative complications are as follows:

- Myocardial ischemia or infarction
- Arrythmia requiring treatment
- Circulatory insufficiency (requiring a vasopressor or inotropic agent infusion for more than 6 hours)
- Ischemic stroke
- Hemorrhagic stroke
- Acute lung injury
- Pulmonary embolism
- Pulmonary infection requiring antibiotic treatment
- Hypoxemia or respiratory insufficiency requiring supportive treatment including intubation, CPAP, BiPAP, high-flow (>10 L/min) face mask or nasal cannula for more than 6 hours
- Acute kidney injury requiring treatment
- Urinary tract infection requiring antibiotic treatment
- Ileus
- Sepsis
- Anastomotic leakage requiring treatment
- Urinary retention requiring treatment
- Pleural or intra-abdominal effusion requiring intervention
- Wound dehiscence requiring intervention
- Bowel obstruction requiring treatment
- Deep venous thrombosis requiring treatment
- Subcutaneous emphysema requiring treatment
- Surgical bleeding or hematoma requiring intervention
- Surgical site infection (superficial or deep, but not organ or space) requiring antibiotic treatment or procedural treatment (not at bedside)
- Surgical site infection (pelvic or intra-abdominal infection or abscess, i.e., organ or space) requiring antibiotic treatment or procedural treatment (not at bedside)

- Delayed emergence requiring treatment

The Clavien-Dindo Classification (https://www.assessurgery.com/clavien-dindo-classification/)

Grades	Definition
Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics and electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside.
Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.
Grade III	Requiring surgical, endoscopic or radiological intervention
- IIIa	Intervention not under general anesthesia
- IIIb	Intervention under general anesthesia
Grade IV	Life-threatening complication (including CNS complications)* requiring IC/ICU-management
- IVa	single organ dysfunction (including dialysis)
- IVb	Multiorgan dysfunction
Grade V	Death of a patient

*brain hemorrhage, ischemic stroke, subarrachnoidal bleeding, but excluding transient ischemic attacks (TIA); IC: Intermediate care; ICU: Intensive care unit.

8.3 Additional outcomes

1) NRS pain score at PACU and 24 hours after surgery;
2) NRS score of subjective sleep quality at 8:00 am of postoperative day 1.

9. Adverse events

9.1 Definition

1) An adverse event indicates any unpredictable, unfavorable medical event that is associated with any medical intervention and occurs during the study period. It can be related to the study protocol or otherwise. It can manifest as any uncomfortable signs (including abnormal laboratory findings), symptoms or transient morbidity;
2) Predicted adverse events in this study:

- Tachycardia: heart rate > 100 beats per minute or, in case of a baseline value > 83 beats per minute, an increase of more than 20% from baseline;
- Hypertension: systolic blood pressure > 160 mmHg or, in case of a baseline value > 133 mmHg, an increase of more than 20% from baseline;
- Bradycardia: heart rate < 55 beats per minute or, in case of a baseline value < 69 beats per minute, a decrease of more than 20% from baseline (before study drug infusion);
- Hypotension: systolic blood pressure < 95 mmHg or, in case of a baseline value < 119 mmHg, a decrease of more than 20% from baseline;

- Recall: the patient remembers the details of the event(s) that occurs during the period when the patient is under appropriate general anesthesia per standard of care.

Note: for heart rate and blood pressure, the average values measured before surgery are used as baseline values.

9.2 Management

1) Therapy will be provided according to standard clinical practice;
2) The study protocol can be stopped temporarily or permanently if considered necessary by the attending anesthesiologist or the principal investigators. The time and reasons of study interruption will be recorded in CRFs.

Management of predicted adverse events in this study:

1) Bradycardia: administration of medication (e.g. atropine iv bolus) and/or adjustment of anesthetic agents;
2) Hypotension: intravenous fluid bolus, administration of medication (vasopressor iv bolus or infusion), and/or adjustment of anesthetic agents;
3) Tachycardia: administration of medication (esmolol or diltiazem) and/or adjustment of anesthetic agents;
4) Hypertension: administration of medication (labetalol or nicardipine) and/or adjustment of anesthetic agents;

9.3 Recording

1) Any adverse event should be documented, including type, timing, duration, management, and sequelae;
2) Any adverse event should be followed up until it is completely resolved or the therapy is terminated.

10. Severe adverse events

10.1 Definition

A severe adverse event indicates any unpredictable medical events that lead to death, threat of life, prolonged length of hospital stay, persistent disability or dysfunction, or other severe event.

10.2 Management

In case of any severe adverse events, the study protocol will be stopped and treatment will be initiated immediately.

10.3 Recording and reporting

1) In case of any severe adverse event, apart from active treatment and record as above, the principal investigator and the Ethics Committee will be informed within 24 hours in written report;
2) In case of study drug related death, immediately stop the clinical trial, report the event to the Ethics Committee as soon as possible, record in detail and carefully preserve the related documents;
3) Any severe adverse event must be followed up until it is completely resolved or the therapy is terminated.

11. Unmask of blinding

For an individual patient, at the completion of the study (30 days after surgery), all data are checked to ensure its quality and input into the database, the database will be locked up and the blindness will be unmasked.

12. Data management

1) Investigators should promptly, completely, and correctly record data in the CRF based on the original observation;
2) The PIs and the study coordinator will monitor if the study is carried out according to the protocol. The completed CRFs, after signed by the PIs, will be sent to the investigator who is responsible for data management;
3) Data input will be performed by an investigator and checked out by another independent investigator. CRFs will be stored in sequential order;
4) Data management can be inspected by the Clinical Research Ethics Committee of both Yale University and Central South University at any time.

13. Statistical analysis

13.1 General principles

1) Numeric variables will be presented as mean (standard deviation) or median (minimum, maximum; or interquartile range). Categorical variables will be presented as number of cases (percentage);
2) Two-tailed tests will be used in all statistical analysis, and a p value of less than 0.05 will be considered to be of statistical significance for the primary outcome. The Benjamini-Hochberge procedure will be applied to control for the multiple testing for all secondary outcomes.

13.2 Patient recruitment and drop-out status

The status of patient recruitment and drop-out will be summarized and listed. Comparison of the overall drop-out rate between the two groups will be performed with chi-square test.

13.3 Patient populations used for analysis

1) The modified intention-to-treat (ITT) population: The modified ITT population includes all patients who undergo randomization, surgery (as long as the skin incision is made), and have the primary outcomes data collected. Patients whose surgery is cancelled or aborted in the middle of surgery (after skin incision) will be included in this population.

   The primary outcome is regarded as not collected in the following situations:
   a) death (within postoperative 5 days);
   b) early hospital discharge (for non-medical reasons and within postoperative 5 days);
   c) intubated/sedated/comatose for more than 24 hours (within postoperative 5 days);
   d) withdraw consent (within postoperative 5 days);
   e) data missing.

2) The per-protocol population: The patients from the modified ITT population will be included in the per-protocol population if they fulfill the eligibility, intervention, and outcome assessment specified by the protocol.

   The following patients are excluded:
   a) ineligible patients
   b) randomization allocation error;
   c) SedLine monitor malfunction (not working at all or >50% of the anesthetic duration (PSI <75) without monitoring data);
   d) SedLine monitor not blinded in the usual care group;
   e) being anesthetized with inhalational anesthetics;
   f) surgery aborted or converted to open.

3) As-treated population from the SedLine-guided care group: This population is a subset of the per-protocol population. For patients from the SedLine-guided care group, they are regarded as fulfilling the as-treated criteria if the below-10 SEF AUC (left + right) is less than 10 (or the median value of the AUC, if AUC < 10 gives less than 300 patients). These patients are regarded as having received effective SedLine-guided intervention. This rule does not apply to patients from the per-protocol population from the usual care group.

13.4 Demographics and baseline characteristics

1) Descriptive statistics of demographic information and baseline characteristics (such as previous history of comorbidity and medication) will be presented;
2) Comparison of baseline numeric variables (such as age, etc.) between groups will be performed with independent sample t-test or Wilcoxon rank sum test. Comparison of categorical variables (such as gender, presence of a comorbidity, etc.) between groups will be performed with chi-square test or Fisher exact test. Information (e.g., p-values) will only be used in selecting covariates for later sensitivity (adjusted) analysis of the primary outcome.

13.5 Effectiveness evaluation

Evaluation of primary endpoint

The incidence of postoperative delirium within 5 days after surgery will be calculated. Comparison between groups will be performed with chi-square or Fisher's exact test. The relative risk and the corresponding 95% confidence interval (CI) will be calculated to measure the magnitude of difference in risk of having postoperative delirium between groups.

Evaluation of secondary endpoints

1) Non-normal continuous endpoints will be analyzed by the Wilcoxon rank sum test. The Hodge-Lehman method will be used to estimate median of between-group difference with 95% CI.
2) Time-to-event variables (length of ICU stay, length of hospital stay) will be analyzed by the Wilcoxon rank sum test or by survival analysis, with difference between groups assessed with Log-Rank test.
3) The incidence of postoperative complications and 30-day mortality will be compared with Chi-square test or Fisher's exact test as appropriate.

Sensitivity analysis

In the ITT dataset, we will perform a sensitivity analysis by fitting a multivariable logistic regression model of the primary outcome with covariate adjustment. Prognostic or risk factors of postoperative delirium shown in previous literature, and baseline and perioperative variables that differed between groups ($p < 0.10$) together with the intervention factor (administration of dexmedetomidine or not) will be entered into the regression model, As the incidence of delirium is not a rare event, the odds ratio (OR) estimate from the logistic regression analysis will possibly overestimate the relative risk (RR) – our measure of effect size in this study, we will convert the OR into RR using the Zhang and Yu method (Zhang J, Yu KF. What's the relative risk? A method of correcting the odds ratio in cohort studies of common outcomes. Jama 1998;280:1690-1)

Subgroup analysis

Subgroup analysis will be based on the ITT dataset per age (<65 years or ≥65 years old), body mass index (< or ≥25), smoker or not, alcoholism or not, Charlson comorbidity score (<2 or ≥2), preoperative MMSE score (<24 or ≥24), diagnosis of the surgical lesion (benign vs. malignant), ASA physical status classification (I-II or III), baseline systolic blood pressure (<130 or ≥130 mmHg), propofol dose used for anesthesia maintenance (divided by the median value), and anesthesia time (divided by the median value).

14. Quality control and quality assurance

14.1 For investigators/care givers

1) Trial protocol will be thoroughly explained to all investigators/care givers before the start of the trial. The trial protocol must be strictly adhered throughout the trial period;
2) All expected and unexpected findings will be documented promptly and correctly in order to guarantee the reliability of the values;

3) The monitors and instruments that are used during the study period will be checked and corrected regularly in order to guarantee their normal function;
4) Data analysis will be performed by the statisticians and investigators;
5) Any conclusions must be derived from the original data.

14.2 For participants

1) Possible benefits and risks associated with the study will be clearly explained to every potential participant;
2) Written informed consent must be signed by every enrolled patient, or by the authorized surrogate of the patient;
3) If the enrolled patients refuse to participate in the study during the study period, the patient will be excluded for further study.

14.3 Study termination

1) If a study-related death occurs during the study period, the study will be stopped. A report will be sent to the Ethics Committee. Restart of the study will need an approval from the Ethics Committee;
2) The study will be terminated after accomplishment of patient recruitment and data collection. Decision will be made by the principal investigator.

15. Ethics requirement and written informed consent

1) Helsinki declaration and Chinese guidelines of Good Clinical Practice will be strictly followed. The study protocol must be approved by the Ethics Committee before the study can be started;

2) For every potential participant, investigators have the responsibilities to fully explain the study purpose, procedures, as well as possible risks in a written informed manner. They must let every potential participant know that he/she has the right to withdraw his/her consent at any time during the study period. Every potential participant must be given a written informed consent. Every participant or the authorized surrogate of the patient must sign the consent before they can be enrolled in the study. Written informed consents will be kept as a part of the clinical trial documents.

16. Preservation of documents

Investigators will carefully preserve all documents and data of the clinical trial according to the Good Clinical Practice requirement.

17. Declaration of interests

None declared.

18. References

Included under each section, respectively.

Section B: Written Informed Consent with Trial Description

"Impact of electroencephalogram – guided anesthetic care on delirium after laparoscopic surgery: a randomized controlled trial"

1. Why do we invite you to participate in this study?

We invite you to participate in this randomized and controlled study investigating the **Impact of electroencephalogram – guided anesthetic care on delirium after laparoscopic surgery**. The study is organized by Yale University Department of Anesthesiology and will be performed in Central South University Xiangya Hospital. We are expected to enroll 1560 participants who are scheduled to undergo elective laparoscopic surgery.

Before you decide to participate in the study, please read the following description carefully which will help you to understand the purpose and contents of the study, to understand the potential benefits from the study that it may bring to you, as well as the potential risks that you may encounter during the study. You are welcome to discuss your concerns with your doctors, relatives and/or friends freely before making the decision. If you have any questions or would like to get more information about the trial, please do contact us.

2. What is the purpose of this study?

We are looking at if the anesthetic care guided by EEG (the electrical activity of the brain) monitoring will lower the chances of having delirium after surgery. Delirium is a common problem after surgery and can often occur in older patient after surgery. It can present as inability to concentrate, disturbances in your perception, changes in your level of consciousness and impairment of your normal thinking. Patients who get delirium after surgery tend to stay in hospitals longer, suffer from more complications and recovery slower than patients who don't get delirium.

We don't know exactly why or how delirium occurs. There are many risk factors. Some are modifiable. Some are not. One of the potential risk factors is deep anesthesia, referring to the overdose of anesthetic drugs. The depth of anesthesia can be assessed using EEG monitoring. However, whether the anesthetic care guided by EEG monitoring can reduce the chance of delirium after surgery is poorly studied. A good quality study is needed to understand if we can reduce delirium via EEG – guided care.

3. Do I have to participate in?

The decision to participate in the study is entirely voluntary. You make the decision to take part in or not, and can withdraw consent at any time without giving any reasons during the study. If you decide to participate, please sign the written informed consent form. You can keep a signed informed consent form and a copy of study description. Withdrawal from the study does not affect your treatments throughout your hospital stay. In such case, your data and information will not be

used in the study. On the other hand, if you or we think the study is affecting your normal treatment or outcome, the researchers will also stop the study.

During the period of study participation, please tell researchers your true medical history and current physical status, as well as whether you have participated in any other studies currently or recently, or if you have any newly developed discomfort. If you do not abide the study protocol or develop any study-related harm, the researchers can terminate your participation in the study.

4. If I participate, what do I need to do?

If you agree to participate in this study, we will give you a recruitment number and establish a research records for you. We will collect your demographic and baseline information before surgery; we will visit you and assess your neurocognitive function after surgery. The occurrence of delirium will be assessed in the post-anesthesia care unit (PACU) and twice daily on postoperative day 1 to 5. Each assessment will last about 5 minutes or less. During the rest period of postoperative hospitalization, we will follow you up daily and record the occurrence of other complications. At 30 days after surgery, we will call you (in case you have been discharged from the hospital) to assess your health status. All the above inspection and assessment are free of charge and the only thing you need to do is to cooperate with our investigators.

5. Will participation in this study bring me extra cost or reward?

The EEG monitoring used in study is free. Participation in the study will not bring you extra cost or gain you any extra rewards.

6. Do I get any benefit from participating in the study?

Participation in the study will help us to understand how to reduce the chance of delirium after surgery. The results of this study will contribute to the improvement of anesthetic practice.

7. What kind of anesthesia will I receive during surgery? What kind of analgesia will I use after the surgery?

Anesthetic regimen will not be changed no matter whether you participate in this study or not during surgery, nor the pain relief strategy after surgery. Participants will be randomly divided into two groups. Patients in the intervention group will receive EEG monitoring and the anesthetic care will be additionally guided by the monitor. Patients in the control group will receive the same EEG monitoring; however, the monitor screen will be covered and blinded to your anesthesiologist. Your anesthesiologist will manage the anesthetic care in a conventional manner. Your assignment to either group will be randomized.

8. Are there any potential risks or adverse effects to me?

The EEG monitor itself is non-invasive. It connects to you via an adhesive probe like a sticker. The potential risks of having this monitor include, even though not reported, skin injury or other unforeseeable events. Any adverse events occurred during the study period will be managed

promptly according to routinely clinical practice. In case of any harmful consequence resulted directly from the study, participant will be compensated according to the corresponding legal provisions.

9. Will my personal information be confidential?

Some data obtained from you during the study will be published in the form of scientific papers, but your personal information (including name, age, education and etc.) will be kept confidential and your personal privacy will be protected according to law. Non-research team personnel will not be allowed to obtain your information, unless permitted by yourself. Your information (recorded in written or other forms) will be preserved for 5 years and then destroyed 5 years after the end of the study. If the information needs to be preserved for more than 5 years, we will obtain your permission by telephone, and will inform you how long and in what way your information will be preserved and used in the future. All research members and institutions involved in the study will maintain confidentiality. In order to ensure that the study is carried out in accordance with the regulations, administrative members or the ethics committee members may access your personal information when necessary.

10. How can I get more information?

If you have any questions about the study, or suffer from any discomfort and injury during the study, or want to obtain more information of the study, please do not hesitate to contact the research members: Lingzhong Meng, MD, E Wang, MD and Adrian Gelb, MB ChB.

If you have any questions regarding the ethical issues of the study, please contact the Clinical Research Ethics Committee at Yale University, Central South University, and University of California San Francisco.

Signature page

Informed consent and signature:

I have read the informed consent for this trial carefully. The study protocol has been explained to me in full detail. I totally understand the purpose and nature of the study, as well as my rights and risks during the study.

I would like to participate in the study voluntarily; and I can confirm that I cooperate with the research members according to the study protocol and the contents listed in informed consent and participate in the trial throughout the entire course of the study.

Patient (or legally authorized representative)

Printed Name (or legally authorized representative):

Signature:

Date:

<Relationship between legally authorized representative and patient (e.g., parent or legal guardian)>

Person Obtaining Consent

Printed Name & Title:

Signature:

Date:

Section C: Neurocognitive and Delirium Assessment

See Supplemental Remarks 2-4

Section D: Definitions of Postoperative Complications

Complications	Definition
Circulatory insufficiency	Requirement of inotropic agents or vasopressors after surgery
Acute myocardial ischemia or infarction	Concentration of cardiac troponin I exceed the diagnostic criteria for myocardial ischemia or infarction as well as new Q waves (lasts for 0.03 s) or continuous (4 days) abnormal ST-T segment
Arrhythmia	Confirmed by 12-lead electrocardiogram and necessitated medical treatment and/or cardioversion
Pulmonary infection	New infiltrate on chest radiograph combined with temperature over 38°C and leukocytosis
Acute respiratory failure	Severe hypoxemia or hypercapnia requiring endotracheal intubation and mechanically assisted ventilation
Stroke	Persisted new focal neurologic deficit and confirmed by neurologic imaging
Acute kidney injury	Creatinine elevation meeting the current diagnostic criteria
Wound infection or dehiscence	Wound infection (purulent discharge or positive bacterial culture) or rupture that required secondary suturing
Ileus	Abdominal distention, bloating, and "gassiness", Diffuse, persistent abdominal pain, Nausea and/or vomiting, Delayed passage of or inability to pass flatus, or Inability to tolerate an oral diet, for more than 3-5 days
Anastomotic leakage	Extravasation of contrast agent in the body cavity or retroperitoneal space that required percutaneous drainage
Severe sepsis	Two or more criteria of systemic inflammatory response syndrome, with known infection and new onset dysfunction of at least one system
Urinary tract infection	Confirmed by urinalysis and urine culture and necessitated antibiotic therapy

Section E: Case Report Form

Impact of electroencephalogram – guided anesthetic care on delirium after laparoscopic surgery: a prospective, randomized and controlled trial

Case Report Form

Initiator: Yale University and Central South University

Research Centers: Central South University, Xiangya Hospital, Changsha, Hunan Province, China

Study Sequence No. _ _ _ _

Medical record No _ _ _ _ _ _ _ _

Date (YYYY-MM-DD) **20** _ _-_ _-_ _

Study Coordinator _____

Anesthesiologist _____

Outcome Assessor-1 _____

Outcome Assessor-2 _____

Illustration

1. This is a prospective, randomized controlled study. All recorded data must be timely, accurate and complete.
2. If error(s) occurs in filling data, please use ONE strikethrough line and refill the correct data, and sign name of the corrector and date of correction. Attention: Do not cover the original data; do not use the eraser or correction fluid; do not cross more than one strikethrough line.
3. Every page and every item of the case report form (CRF) must be completed. Fill "√" in the "□" to indicate selection; "UK" to indicate "do not know" or "unknown", "NA" to indicate "cannot provide" or "not applicable".
4. Patient's abbreviated name (initials of the last and first name) will be recorded in the form of left aligned acronym of Chinese phonetic alphabet. For example:
   Zhang Wei will be recorded as: ZW;
   Zhang Xiao-Wei will be recorded as: ZXW;
   Ou-Yang Xiao-Wei will be recorded as: OYXW.
   For studies in the USA, the initial of the first name is placed before the initial of the last name. For example:
   John Webber will be recorded as: JW (John is the first name).
5. The number of recruited patients will be recorded in four numbers. For example:
   No. 1 will be recorded as: 0001;
   No. 12 will be recorded as: 0012;
   NO. 123 will be recorded as: 0123;
   NO. 1234 will be recorded as: 1234.
6. Numeric data such as body weight and height will be recorded with one decimal, for example:
   Body weight 65 kg will be recorded as: 65.0 kg;
   Height 165.5 cm will be recorded as: 165.5 cm.
7. Date will be recorded as year-month-day, for example:
   January 1st of 2016 will be recorded as: 2016-01-01;
   December 16th of 2016 will be recorded as: 2016-12-16.
8. Duration of education is the actual years of education.
9. The time will be recorded in the form of hh:mm, and use a 24-hour clock. For example:
   9:35 in the morning will be recorded as: 09:35;
   2:05 in the afternoon will be recorded as: 14:05.
10. If investigators have any questions during the study period, please contact the principle investigator (Prof. E Wang or Prof. Lingzhong Meng). In case of severe adverse events which must be recorded, responsible investigator must report to the supervising authorities including the principal investigators and the Ethics Committees within 24 hours.

Contact numbers for reporting serious adverse events:

Responsible parties	Contact numbers
*Principal investigator: Prof. Lingzhong Meng, Department of Anesthesiology, Yale University	(949) 732-8811 (USA)
*Principal investigator: Prof. E Wang, Department of Anesthesiology, Central South University Xiangya Hospital	
*Clinical Research Ethics Committee, Central South University Xiangya Hospital	
*Department of Drug Safety Supervision, Hunan Municipal Food and Drug Administration	
*Department of Drug Research and Supervision, Division of Safety Supervision, State Food and Drug Administration	

(Attention: Severe adverse events must be reported within 24 hours!)

Flow chart of the study

	Screen	Recruitment	Intraoperative	Postoperative follow-up							
				PACU	D1	D2	D3	D4	D5	D6-discharge	D30±3
Inclusion/exclusion criteria	X	X									
Informed consent	X										
Demographic data	X	X									
Preoperative diagnosis	X	X									
Previous medical history	X	X									
Physical examination	X	X									
Auxiliary examination	X	X									
MMSE	X	X									
Baseline CAM	X	X									
Anesthesia			X								
Study protocol execution		X	X	X	X	X	X	X	X	X	X
Delirium assessment*				X	X	X	X	X	X		
Adverse events				X	X	X	X	X	X	X	
NRS of severity of pain				X	X						
NRS of subjective sleep quality					X						
Use of other drugs				X	X	X	X	X	X	X	
Postoperative complications**				X	X	X	X	X	X	X	X
All-cause 30-day mortality											X

*Delirium will be assessed at PACU and twice daily (8:00-10:00 am and 18:00-20:00 pm) during postoperative day 1 to 5.
**Patients will be followed up until postoperative day 30.

Inclusion Criteria:

Age ≥ 50 years	Y□	N□
ASA physical score I-III	Y□	N□
Scheduled to undergo elective laparoscopic surgery under general anesthesia with endotracheal intubation	Y□	N□
Able to undergo MMSE and CAM assessment	Y□	N□
Extubation expected after surgery	Y□	N□
Scheduled to stay in hospital > 3 days after surgery	Y□	N□

*Subjects cannot be enrolled in the study if any one of the above is "N"

Exclusion Criteria:

Refuse to participate	Y□	N□
Emergent surgery or trauma patients	Y□	N□
Preoperative cognitive impairment characterized by MMSE of 23 or less	Y□	N□
Preoperative history of stroke, TIA, schizophrenia, Parkinson's disease, epilepsy, or dementia	Y□	N□
Inability to communicate in the preoperative period due to language difficulties, or significant hearing or visual impairment	Y□	N□
Severe cardiac disease including low-output cardiac failure defined as a preoperative left ventricular ejection fraction < 30% or arrhythmia with pacemaker or AICD placement	Y□	N□
Severe hepatic dysfunction being evaluated for liver transplantation or with a Child-Pugh Class C classification	Y□	N□
Severe renal dysfunction requiring renal replacement therapy before surgery	Y□	N□
Those with preoperative ASA classification of 4 or who are unlikely to survive for more than 24 hours after surgery	Y□	N□

*Subjects cannot be enrolled if anyone of the above is "Y"

Baseline information and medical history

Abbreviated name:	**Gender:** □ Male; □ Female	**Nationality:**
Occupation:	**Marital status:** □ Married; □ Unmarried; □ Others	**Age (years):**
Date of birth (YYYY-MM): 19_ _ - _ _	**Height:** _ _ _. _ cm	**Weight:** _ _ _. _ kg
Highest degree of education: □ No school; □ Elementary school; □ Middle school; □ High School; □ College; □ Master degree; □ Doctor degree		
Duration of education: _ _ years		
Date of hospital admission: 20_ _ - _ _ - _ _		
Preoperative surgical diagnosis:		
Surgery being scheduled: □ Stomach; □ Colorectal; □ Small intestine; □ Liver; □ Pancreas; □ Gallbladder; □ Kidney; □ Bladder; □ Retroperitoneal; □ Combined; □ Other (please specify: _____)		
ASA physical classification: □ ASA I: No organic pathology or patients in whom the pathological process is localized and does not cause any systemic disturbance or abnormality; □ ASA II: A patient with mild systemic disease that results in no functional limitation; □ ASA III: A patient with severe systemic disease that results in functional impairment; □ ASA IV: Severe systemic disease that is a constant threat to life; □ ASA V: Moribund condition in a patient who is not expected to survive without the operation.		

Medication within one month (including sedatives, analgesics and anticholinergics)

Drug	**Dose**	**Route**	**Frequency**

Most recent preoperative blood/biochemical examination

Hb (g/L)		Na (mmol/L)	
Hct (%)		K (mmol/L)	
Platelet		Cr (umol/L)	
INR		BUN (mmol/L)	
ALB (g/L)		ALT (IU/L)	
GLU (mmol/L)		AST (IU/L)	
HbA1c			

Preoperative comorbidity	Cognitive function	MMSE Score: ___; □ Dementia		
	Neuropsychiatric diagnosis	□ None; □ Stroke; □ TIA; □ Schizophrenia; □ Parkinson's disease; □ Epilepsy; □ Depression		
	Cardiovascular system	□ None; □ CAD; □VHD; □ Congenital heart disease; □ Hypertension; □ Arrhythmia; □ Cardiomyopathy; □ Others: _____		
		□ **Current NYHA classification:** ____ □ I: No symptoms and no limitation in ordinary physical activity, e.g. no shortness of breath when walking, climbing stairs etc. □ II: Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity. □ III: Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g. walking short distances (20–100 m). Comfortable only at rest. □ IV: Severe limitations. Experiences symptoms even at rest. Mostly bedbound patients.		
	Respiratory system	□ None; □ COPD; □ Chronic bronchitis; □ Asthma; □ Smoke (>10 cigarettes/d, > 1 year), ____ packs/d, _____ years □ Others: _____		
	Metabolic disorders	□ None; □ Diabetes; □ Thyroid disease; □ Hyperlipidemia; □ Hepatic dysfunction (ALT and/or AST ≥ 5 times of upper limit); □ Renal dysfunction (Cr ≥ 177 μmol/L); □ Electrolyte disorder; □ Morbid obesity; **BMI ____** □ Others: _____		
	Others	□ Alcoholism* _____ ml/day; _____ years □ GI disorders; □ AIDS; □ Cancer □ History of allergy: _____ □ Others: _____		
History of surgery	□ No			
	□ Yes	Date	Surgery	Anesthesia

*Two drinks or more daily, or weekly consumption of the equivalent of 150 ml of alcohol.

Updated Charlson Comorbidity Index Score = _____

Comorbidity	**Charlson weight score**	**Score of the patient**
Myocardial infarction	0	
Congestive heart failure	2	
Peripheral vascular disease	0	
Cerebral vascular disease	0	
Dementia	2	
Chronic lung disease	1	
Rheumatic diseases	1	
Ulcer of digestive tract	0	
Mild liver disease	2	
Diabetes without chronic complications	0	
Diabetes with chronic complications	1	
Hemiplegia or paraplegia	2	
Renal disease	1	
Malignant tumor (including leukemia and lymphoma)	2	
Moderate / severe liver disease	4	
Metastasis of solid tumors	6	
AIDS/HIV	4	
Total score	**24**	

Quan H, Li B, Couris CM, Fushimi K, Graham P, Hider P, Januel JM, Sundararajan V. Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. Am J Epidemiol. 2011;173(6):676-82.

Preoperative drugs

Use of sedatives & analgesics during the night before surgery: □ No; □ Yes			
Check if yes	Drug	Dose	Route
□			
□			
□			
Premedications: □ No; □ Yes			
Check if yes	Drug	Dose	Route
□	Scopolamine		
□	Atropine		
□	Glycopyrrolate		
□	Midazolam		
□	Other:		
□	Other:		
□	Other:		

Intraoperative

Date of surgery (YYYY-MM-DD): 20_ _ - _ _ - _ _
Name of surgery: _____

Anesthesia techniques and drug details

□ GA; □ Combined GA-epidural; □ Other: _____

Anesthesia induction (HH:MM): _ _: _ _
Extubation (HH:MM): _ _: _ _
Duration of anesthesia (from anesthesia induction to extubation): _ _ _ mins

Skin incision (HH:MM): _ _: _ _
Skin closure (HH:MM): _ _: _ _
Duration of surgery (from skin incision to closure): _ _ _ mins

Anesthesia induction

Check if yes	*Drug*	*Dose*	*Route*
□	Lidocaine		
□	Propofol		
□	Sufentanil		
□	Rocuronium		
□	Fentanyl		
□	Succinylcholine		
□	Midazolam		
□	Morphine		
□	Etomidate		
□	Other:		
□	Other:		

Anesthesia maintenance

Check if yes	*Drug*	*Dose*	*Route*
□	Propofol		infusion
□	Remifentanil		infusion
□	Sufentanil		
□	Sevoflurane		
□	Dexmedetomidine		
□	Fentanyl		
□	Morphine		
□	Rocuronium		
□	Vecuronium		
□	Cisatracurium		
□	Other:		
□	Other:		

Epidural drugs

Check if yes	*Drug*	*Dose*	*Route*
□	Lidocaine		
□	Ropivacaine		
□	Bupivacaine		
□	Fentanyl		
□	Other:		
□	Other:		

Other drugs

Check if yes	*Drug*	*Dose*	*Route*
□	Dexamethasone		
□	Methylprednisolone		
□	Hydrocortisone		
□	Ondansetron		
□	Tropisetron		
□	Atropine		
□	Glycopyrrolate		
□	Scopolamine		
□	Neostigmine		
□	Penehyclidine		
□	Other:		
□	Other:		

Intraoperative inputs

Check if yes	*Name*	*Total volume (mL)*
□	0.9% NS	
□	LR	
□	Plasmalyte	
□	5% Albumin	
□	Colloid: _____	
□	PRBC	
□	FFP	
□	Platelet	
□	Cellsaver	
□	Other:	
□	Other:	
□	Other:	
□	Other:	
□	Other:	
□	Other:	

Intraoperative outputs

Check if yes	*Name*	*Total volume (mL)*
□	Estimated blood loss	
□	Urine output	
□	Other:	
□	Other:	
Lowest hemoglobin (Hb) level during surgery if available _ _. _ (g/L)		
Highest lactate level during surgery if available _ _. _ (mmol/L)		
Procedure converted to open surgery: Yes □; No □; Reason: _____		
Procedure aborted: Yes □; No □; Reason: _____		

Postoperative

Extubation at the end of surgery: □ Yes; □ No			
PACU admission: □ Yes; □ No			
Date (YYYY-MM-DD): 20 _ _ - _ _ - _ _	Time in (hh: mm): _ _ : _ _	Time out (hh: mm): _ _ : _ _	PACU length: _ _ _ mins
ICU admission: □ Yes; □ No			
Date (YYYY-MM-DD) in: 20 _ _ - _ _ - _ _	Time in (hh: mm) _ _ : _ _	Date (YYYY-MM-DD) out: 20 _ _ - _ _ - _ _	ICU days: _ _ days
Details of extubation if not extubated at the end of surgery in the Operating Room			
Location: □ PACU; □ ICU			
Duration from the end of surgery to extubation: _ _ hours, or, _ _ days			

Delirium Assessment (performed at both PACU and floor/ICU)

Date	Time	RASS	Feature 1:	Feature 2:	Feature 3:	Feature 4:	Delirium
		-5 to +4	**Acute Onset or Fluctuating Course**	**Inattention**	**Altered Level of Consciousness**	**Disorganized Thinking**	**Diagnosis**
PACU	30 mins after extubation to Discharge		□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No
POD 1	8:00-10:00		□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No
	16:00-18:00		□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No
POD 2	8:00-10:00		□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No
	16:00-18:00		□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No
POD 3	8:00-10:00		□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No
	16:00-18:00		□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No
POD 4	8:00-10:00		□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No
	16:00-18:00		□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No
POD 5	8:00-10:00		□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No
	16:00-18:00		□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No

Diagnosis of Emergence Delirium: □ Yes □ No

Diagnosis of POD: □ Yes □ No

Record of adverse events

An adverse event indicates any unpredictable, unfavorable medical event that is associated with any medical intervention and occurs during the study period. It can be related to the study or not.

A severe adverse event indicates any unpredictable medical events that lead to death, threat to life, prolonged length of stay in hospital, persistent disability or dysfunction, or other severe results.

Any adverse event should be followed up until it is completely resolved or therapy terminated.

Is there any new adverse event within 24 hours after surgery: □Yes; □No
Is there any new severe adverse event within 3 days after surgery: □Yes; □No
(Report form of severe adverse event see attached table)

	Start time	End time	Diagnostic evidence	Mode of occurrence	Is it severe adverse event?	Treatment[1]	Outcome[2]	Related to study?
Recall[3]				□ Persistent □ Transient	□ Yes □ No			□ Yes □ No
Hypotension[4]				□ Persistent □ Transient	□ Yes □ No			□ Yes □ No
Bradycardia[5]				□ Persistent □ Transient	□ Yes □ No			□ Yes □ No
Hypertension[6]				□ Persistent □ Transient	□ Yes □ No			□ Yes □ No
Tachycardia[7]				□ Persistent □ Transient	□ Yes □ No			□ Yes □ No
Hypoxemia[8]				□ Persistent □ Transient	□ Yes □ No			□ Yes □ No
Other:				□ Persistent □ Transient	□ Yes □ No			□ Yes □ No
Other:				□ Persistent □ Transient	□ Yes □ No			□ Yes □ No
Other:				□ Persistent □ Transient	□ Yes □ No			□ Yes □ No

[1]Treatment refers to any intervention that intends to reverse or treat the adverse event;
[2]Outcomes include: A=Recovered, B=Deteriorated, C=Persist, D=Recovered but with sequelae, E=Fatal, F=No follow-up (reasons must be explained);
[3]Recall means the patient can recall the surroundings or an event related to the surgery while under general anesthesia.
[4]Defined as SBP< 90 mmHg or a decrease of more than 20% from the baseline value;
[5]Defined as HR< 50 bpm or a decrease of more than 20% from the baseline value;
[6]Defined as SBP> 160 mmHg or an increase of more than 20% from baseline;
[7]Ddefined as HR > 100 bpm or an increase of more than 20% from baseline;
[8]Defined as SpO_2 < 90%.

NRS of pain severity
(0 = no pain and 10 = the worst possible pain)

	PACU	24 hours after surgery
Score		

Use patient-controlled analgesia pump after surgery

□ No □ Yes		
□ PCIA	□ Morphine □ Sufentanil □ Others	**Total dose within 24 hours:**
□ PCEA	□ Sufentanil 125ug+1% ropivacaine 30ml)/250ml □ Others	**Total dose within 24 hours:**

Analgesics and other drugs administered during the first 7 days after surgery

(Route of administration to be documented)

Drug	Day of surgery	POD 1	POD 2	POD 3	POD 4	POD 5	POD 6	POD 7
□ Fentanyl (mcg)								
□ Morphine (mg)								
□ Sufentanil (mcg)								
□ Hydromorphone (mg)								
□ Meperidine (mg)								
□ Midazolam (mg)								
□ Flurbiprofen (mg)								
□ Parecoxib (mg)								
□ Penehyclidine hydrochloride (mg)								
□ Scopolamine (mg)								
□ Atropine (mg)								
□ Glycopyrrolate (mg)								
□ Hydrocortisone (mg)								
□ Dexamethasone (mg)								
□ Methylprednisolone (mg)								
□ Other:								
□ Other:								
□ Other:								
□ Other:								
□ Other:								
□ Other:								
□ Other:								
□ Other:								
□ Other:								
□ Other:								
□ Other:								
□ Other:								
□ Other:								

Note: Record the daily consumption at 18:00 pm. For patients who are admitted after 18:00 pm, record the daily consumption at the next 18:00 pm.

Postoperative complications
(Patients will be followed up until 30 days after surgery; diagnostic criteria listed in brackets)

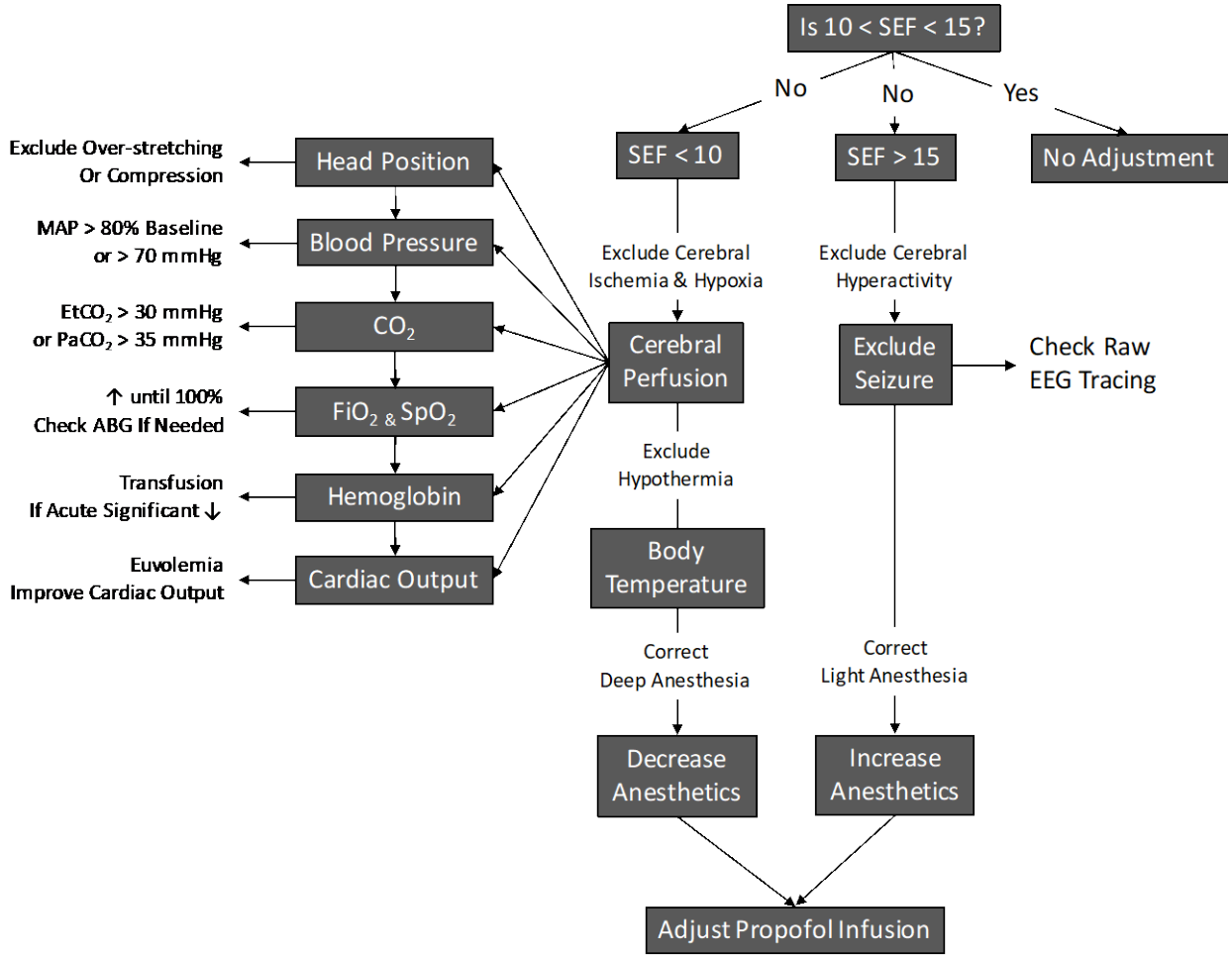
Complications of organs/systems		**Diagnostic Evidence**
□ Respiratory insufficiency (hypoxemia or hypercapnia, requiring mechanical ventilation for any duration after surgery)	□ Yes □ No	
□ Pulmonary embolism (confirmed by clinical manifestations and imaging study)	□ Yes □ No	
□ Acute myocardial infarction [increase of troponin T concentration above the hospital laboratory's myocardial infarction threshold and either new Q waves (duration of at least 0.03 seconds) or persistent changes (4 days) in ST-T segment]	□ Yes □ No	
□ Circulatory insufficiency (requirement of inotropic agents or vasopressors for any duration after surgery)	□ Yes □ No	
□ New onset arrhythmia (confirmed by 12-leads electrocardiography and necessitating medical treatment and/or cardioversion)	□ Yes □ No	
□ Stroke (persisted new focal neurologic deficit and confirmed by neurologic imaging)	□ Yes □ No	
□ Acute kidney injury (KDIGO defines AKI as any of the following: • Increase in serum creatinine by 0.3mg/dL or more within 48 hours or • Increase in serum creatinine to 1.5 times baseline or more within the last 7 days or • Urine output less than 0.5 mL/kg/h for 6 hours)	□ Yes □ No	□ Baseline Cr: ___ □ Peak Cr within 48 hours: ___ □ Peak Cr within 7 days: ___ □ Urine output: ___ mL/kg/h for ___ hours
□ Deep vein thrombosis (confirmed by venous ultrasonography/venography)	□ Yes □ No	
□ Disseminated intravascular coagulation (manifestation of abnormal bleeding, together with prolonged PT/aPTT, declined platelet/fibrinogen levels, as well as increased fibrin degradation products (including D-dimer))	□ Yes □ No	
□ Ileus (at least one for each of the two following criteria: (1) presence of vomiting OR abdominal distension and (2) absence of flatus/stool OR not tolerating oral diet, in the absence of any precipitating complications)	□ Yes □ No	
Surgical complications		**Diagnostic Evidence**
□ Wound dehiscence (wound rupture that required secondary suturing)	□ Yes □ No	
□ Incisional hernia (requirement of secondary surgery)	□ Yes	

	□ No	
□ Surgical bleeding (bleeding after surgery that required secondary surgical hemostasis)	□ Yes □ No	
□ Anastomotic leakage (extravasation of contrast agent in the body cavity or retroperitoneal space that required percutaneous drainage)	□ Yes □ No	
□ Gastrointestinal hemorrhage (decrease of hemoglobin level combined with positive occult blood test results that required treatment)	□ Yes □ No	
□ Delayed oral intake (lack of bowel movement, flatulence, and requirement of intravenous fluid therapy for more than one week after surgery)	□ Yes □ No	
Infectious complications		**Diagnostic Evidence**
□ Severe sepsis/septic shock (two or more criteria of systemic inflammatory response syndrome, with known infection and new onset dysfunction of at least one system or requirement of vasopressors to maintain blood pressure)	□ Yes □ No	
□ Intra-abdominal abscess (confirmed by ultrasonography or CT scan and required percutaneous drainage)	□ Yes □ No	
□ Pulmonary infection (new infiltrate on chest radiograph combined with temperature of over 38°C and leukocytosis)	□ Yes □ No	
□ Wound infection (pus expressed from the incision, and bacteria cultured from the pus)	□ Yes □ No	
□ Urinary tract infection (confirmed by urinalysis and urine culture and necessitated antibiotic therapy)	□ Yes □ No	
Other complications	**Time of earliest diagnosis**	**Diagnostic Evidence**
□		
□		

Hospital discharge information

Discharge from hospital, date (YYYY-MM-DD)	20 _ _-_ _-_ _
Actual duration of hospitalization (days) based on discharge from hospital	___ days
Postoperative diagnosis (including pathological diagnosis, metastasis and tumor stage information)	
Survival at 30 days after surgery	□Yes; □ No If death within 30 days, date of death: 20_ _ - _ _ - _ _ That is _ _ days after surgery Cause of death:
Hospital readmissions within 30 days after surgery	□Yes; □ No If readmission within 30 days, date: 20_ _ - _ _ - _ _ That is _ _ days after surgery Cause of readmission:

Supplemental remark 1. SedLine-Guided Intervention Flow Chart



Supplemental remark 2. Mini-Mental State Examination (MMSE)
(A Chinese version is needed.)

MMSE to be assessed within 48 hours before surgery and on POD 7 or before discharge.

Instructions: Score one point for each correct response within each question or activity.

Patient name: **Study sequence #**:			
Date of surgery: 20_ _ - _ _ - _ _			
Date of the 1st test: 20_ _ - _ _ - _ _; Date of the 2nd test: 20_ _ - _ _ - _ _			
Maximum Score	**Questions**	**Patient's Score**	
		Pre-op	**POD 5**
5	"What is the year? Season? Date? Day? Month?"		
5	"Where are we now? State? County? Town/city? Hospital? Floor?"		
3	The examiner names three unrelated objects clearly and slowly, then the instructor asks the patient to name all three of them. The patient's response is used for scoring. The examiner repeats them until patient learns all of them, if possible.		
5	"I would like you to count backward from 100 by sevens." (93, 86, 79, 72, 65, …) Alternative: "Spell WORLD backwards." (D-L-R-O-W)		
3	"Earlier I told you the names of three things. Can you tell me what those were?"		
2	Show the patient two simple objects, such as a wristwatch and a pencil, and ask the patient to name them.		
1	"Repeat the phrase: 'No ifs, ands, or buts.'"		
3	"Take the paper in your right hand, fold it in half, and put it on the floor." (The examiner gives the patient a piece of blank paper.)		
1	"Please read this and do what it says." (Written instruction is "Close your eyes.")		
1	"Make up and write a sentence about anything." (This sentence must contain a noun and a verb.)		
1	"Please copy this picture." (The examiner gives the patient a blank piece of paper and asks him/her to draw the symbol below. All 10 angles must be present and two must intersect.)		
30	**Total**		

Folstein MF, Folstein SE, McHugh PR: "Mini-mental state: A practical method for grading the cognitive state of patients for the clinician." J Psychiatr Res 1975;12:189-198.

Supplemental remark 3.
The Confusion Assessment Method (CAM) Instrument for patients NOT in ICU
(A Chinese version is needed.)

Aspects	Assessments	Conclusion									
		Day-1		Day-2		Day-3		Day-4		Day-5	
		AM	PM	AM	PM	AM	PM	AM	PM	AM	PM
1. [Acute Onset]	Is there evidence of an acute change in mental status from the patient's baseline?	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No
2A. [Inattention]	Did the patient have difficulty focusing attention, for example, being easily distractible, or having difficulty keeping track of what was being said?	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No
2B. (If present or abnormal)	Did this behavior fluctuate during the interview, that is, tend to come and go or increase and decrease in severity?	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No
3. [Disorganized thinking]	Was the patient's thinking disorganized or incoherent, such as rambling or irrelevant conversation, unclear or illogical flow of ideas, or unpredictable switching from subject to subject?	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No
4. [Altered level of consciousness]	Overall, how would you rate this patient's level of consciousness? (Alert [normal]; Vigilant [hyperalert, overly sensitive to environmental stimuli, startled very easily], Lethargic [drowsy, easily aroused]; Stupor [difficult to arouse]; Coma; [unarousable]; Uncertain)	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No
5. [Disorientation]	Was the patient disoriented at any time during the interview, such as thinking that he or she was somewhere other than the hospital, using the wrong bed, or misjudging the time of day?	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No

6. [Memory impairment]	Did the patient demonstrate any memory problems during the interview, such as inability to remember events in the hospital or difficulty remembering instructions?	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No
7. [Perceptual disturbances]	Did the patient have any evidence of perceptual disturbances, for example, hallucinations, illusions or misinterpretations (such as thinking something was moving when it was not)?	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No
8A. [Psychomotor agitation]	At any time during the interview did the patient have an unusually increased level of motor activity such as restlessness, picking at bedclothes, tapping fingers or making frequent sudden changes of position?	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No
8B. [Psychomotor retardation]	At any time during the interview did the patient have an unusually decreased level of motor activity such as sluggishness, staring into space, staying in one position for a long time or moving very slowly?	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No
9. [Altered sleep-wake cycle]	Did the patient have evidence of disturbance of the sleep-wake cycle, such as excessive daytime sleepiness with insomnia at night?	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No

The Confusion Assessment Method (CAM) Diagnostic Algorithm

Features	Description & Assessments	Conclusion									
		Day-1		Day-2		Day-3		Day-4		Day-5	
		AM	PM	AM	PM	AM	AM	PM	AM	PM	AM
Feature 1: Acute Onset and Fluctuating Course	This feature is usually obtained from a family member or nurse and is shown by positive responses to the following questions: Is there evidence of an acute change in mental status from the patient's baseline? Did the (abnormal) behavior fluctuate during the day, that is, tend to come and go, or increase and decrease in severity?	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No
Feature 2: Inattention	This feature is shown by a positive response to the following question: Did the patient have difficulty focusing attention, for example, being easily distractible, or having difficulty keeping track of what was being said?	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No
Feature 3: Disorganized thinking	This feature is shown by a positive response to the following question: Was the patient's thinking disorganized or incoherent, such as rambling or irrelevant conversation, unclear or illogical flow of ideas, or unpredictable switching from subject to subject?	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No
Feature 4: Altered Level of consciousness	This feature is shown by any answer other than "alert" to the following question: Overall, how would you rate this patient's level of consciousness? (alert [normal]), vigilant [hyperalert], lethargic [drowsy, easily aroused], stupor [difficult to arouse], or coma [unarousable])	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No

Is the patient delirious?	The diagnosis of delirium by CAM requires the presence of **features 1 and 2 and either 3 or 4**.	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No

Inouye SK, van Dyck CH, Alessi CA, Balkin S, Siegal AP, Horwitz RI. Clarifying confusion: the confusion assessment method. A new method for detection of delirium. Ann Intern Med. 1990;113(12):941-8.

Supplemental remark 4.
CAM-ICU Worksheet for patients in PACU and ICU

The first step, assess the sedation state using Richmond Agitation Sedation Scale (RASS)

Richmond Agitation Sedation Scale (RASS)

Score	Term	Description
+4	Combative	Overtly combative, violent, immediate danger to staff
+3	Very agitated	Pulls or removes tube(s) or catheter(s); aggressive
+2	Agitated	Frequent non-purposeful movement, fights ventilator
+1	Restless	Anxious but movements not aggressive or vigorous
0	Alert and calm	
-1	Drowsy	Not fully alert, but has sustained awakening (eye opening/eye contact) to voice (10 seconds)
-2	Light sedation	Briefly awakens with eye contact to voice (less than 10 seconds)
-3	Moderate sedation	Movement or eye opening to voice (but no eye contact)
-4	Deep sedation	No response to voice, but movement or eye opening to physical stimulation
-5	Unarousable	No response to voice or physical stimulation

Procedure for RASS Assessment

Steps	Patient	Score
Observe patient	Patient is alert, restless, or agitated	0 to +4
If not alert, state patient's name and say to open eyes and look at speaker	Patient awakens with sustained eye opening and eye contact	-1
	Patient awakens with eye opening and eye contact, but not sustained	-2
	Patient has any movement in response to voice but no eye contact	-3
When no response to verbal stimulation, physically stimulate patients by shaking shoulder and/or rubbing sternum	Patient has any movement to physical stimulation	-4
	Patient has no response to any stimulation	-5

Patient RASS Scores

Location/date	PACU	POD-1		POD-2		POD-3		POD-4		POD-5	
Time		AM	PM	AM	PM	AM	PM	AM	PM	AM	PM
Score											

If the RASS score is > -4 (-3 through +4), delirium is assessed using the CAM-ICU Worksheet
CAM-ICU Worksheet

Features	Score	Check here if present
Feature 1: Acute Onset or Fluctuating Course		
Is the patient different than his/her baseline mental status? ***OR*** Has the patient had any fluctuation in mental status in the past 24 hours as evidenced by fluctuation on a sedation/level of consciousness scale (i.e., RASS/SAS), GCS, or previous delirium assessment?	Either question Yes	□
Feature 2: Inattention		
Letters Attention Test (See training manual for alternate **Pictures**) Directions: Say to the patient, "*I am going to read you a series of 10 letters. Whenever you hear the letter 'A,' indicate by squeezing my hand*." Read letters from the following letter list in a normal tone 3 seconds apart. **S A V E A H A A R T** or **C A S A B L A N C A** or **A B A D B A D A A Y** Errors are counted when patient fails to squeeze on the letter "A" and when the patient squeezes on any letter other than "A."	Number of Errors >2	□
Feature 3: Altered Level of Consciousness		
Present if the Actual RASS score is anything other than alert and calm (zero)	RASS anything other than zero	□
Feature 4: Disorganized Thinking		
Yes/No Questions (Use group A or group B to test, if necessary, group A and B can be used interchangeably) **Group A:** 1. Will a stone float on water? 2. Are there fish in the sea? 3. Does one pound weigh more than two pounds? 4. Can you use a hammer to pound a nail? Group B: 1. Will a leaf float on water? 2. Are there elephants in the sea? 3. Does two pounds weigh more than one pound? 4. Can you use a hammer to saw wood?	Combined number of errors >1	□

Errors are counted when the patient incorrectly answers a question. **Command** Say to patient: *"Hold up this many fingers"* (Hold 2 fingers in front of patient) *"Now do the same thing with the other hand"* (Do not repeat number of fingers) *If the patient is unable to move both arms, for 2nd part of command ask patient to *"Add one more finger"* **An error is counted if patient is unable to complete the entire command.**			
Overall CAM-ICU **Feature 1 plus 2 and either 3 or 4 present = CAM-ICU positive**	**Criteria Met**	**□CAM-ICU Positive (Delirium Present)**	
	Criteria Not Met	**□CAM-ICU Negative (No Delirium)**	

Patient CAM-ICU Assessment

Location/date	**PACU**	**POD-1**		**POD-2**		**POD-3**		**POD-4**		**POD-5**	
Time		AM	PM	AM	PM	AM	PM	AM	PM	AM	PM
Positive/ negative	□ **P** □ **N**	□ **P** □ **N**	□ **P** □ **N**	□ **P** □ **N**	□ **P** □ **N**	□ **P** □ **N**	□ **P** □ **N**	□ **P** □ **N**	□ **P** □ **N**	□ **P** □ **N**	□ **P** □ **N**

References:

Sessler CN, Gosnell MS, Grap MJ, Brophy GM, O'Neal PV, Keane KA, Tesoro EP, Elswick RK. The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care unit patients. Am J Respir Crit Care Med. 2002;166(10):1338-44.

Ely EW, Truman B, Shintani A, Thomason JW, Wheeler AP, Gordon S, Francis J, Speroff T, Gautam S, Margolin R, Sessler CN, Dittus RS, Bernard GR. Monitoring sedation status over time in ICU patients: reliability and validity of the Richmond Agitation-Sedation Scale (RASS). JAMA. 2003;289(22):2983-91.

Ely EW, Inouye SK, Bernard GR, Gordon S, Francis J, May L, Truman B, Speroff T, Gautam S, Margolin R, Hart RP, Dittus R. Delirium in mechanically ventilated patients: validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). JAMA. 2001;286(21):2703-10.

Supplemental remark 4. Child-Pugh Grade

Child-Pugh grade A, 5 to 6 points; grade B, 7 to 9 points; grade C, 10 to 15 points.

Index	**Abnormal degree score**		
	1	**2**	**3**
Hepatic encephalopathy*	No	1-2	3-4
Ascites**	No	Light	Moderate or severe
Serum bilirubin (μmol/L)	<34.2	34.2-51.3	>51.3
Serum albumin (g/L)	≥35	28-34	<28
PT (second)	≤14	15-17	≥18

*Hepatic encephalopathy: grade 1, prodromal stage; grade 2, precoma; grade 3, comatose; grade 4, coma.
**Ascites: light, shifting dullness below the midaxillary line; moderate, shifting dullness between the midclavicular line and midaxillary line; severe, shifting dullness beyond the midclavicular line.

Supplemental remark 5. Serious Adverse Event (SAE)

<table>
<tr><td>Report type</td><td>□ 1st time report
□ Follow-up report
□ Summary report</td><td>Report date: 20_ _-_ _-_ _</td></tr>
<tr><td>Trial center name:</td><td>Contact person:</td><td>Tel:</td></tr>
<tr><td>Trial headquarter</td><td>Yale University Dept. of Anesthesiology</td><td>203.785.2802
203.785.6664
anesthesiology@yale.edu</td></tr>
<tr><td>Trial title</td><td colspan="2">Impact of electroencephalogram – guided anesthetic care on delirium after intra-abdominal surgery: a randomized and controlled trial</td></tr>
<tr><td rowspan="3">Subject (patient)</td><td>Abbrev. name:</td><td>Study sequence #:</td></tr>
<tr><td>Gender: □ M □ F</td><td>Date of birth: 20 _ _-_ _-_ _</td></tr>
<tr><td colspan="2">Diagnosis:</td></tr>
<tr><td>Situation of SAE</td><td colspan="2">□ Prolong hospitalization; □ Dysfunction; □ Endanger life;
□ Death; □ Others (please specify _____)</td></tr>
<tr><td colspan="3">Date of occurrence: 20 _ _-_ _-_ _</td></tr>
<tr><td>Management of study protocol</td><td colspan="2">□ Continue; □ Protocol revision; □ Temporary suspension;
□ Permanent suspension</td></tr>
<tr><td>Outcome of SAE</td><td colspan="2">□ Symptoms subsided (sequela □ Yes; □ No)
□ Symptoms continued
□ Death (date of death: 20 _ _-_ _-_ _)</td></tr>
<tr><td>Relationship of SAE with the study</td><td colspan="2">□ Certainly related; □ Possibly related;
□ Possibly unrelated; □ Unrelated;
□ Cannot determine</td></tr>
<tr><td>Previously reported SAE</td><td colspan="2">In China: □ Yes □ No □ Unknown
Outside China: □ Yes □ No □ Unknown</td></tr>
<tr><td colspan="3">Occurrence and treatment of SAE in detail:</td></tr>
</table>

Date is recorded as YYYY-MM-DD

Department of reporter:	
Name of reporter:	
Signature of reporter:	

Section F: Baseline demographics and characteristics

	Intervention (n=)	**Control (n=)**	**p value**
Age (year)			
Male (n=)			
BMI (kg/m^2)			
Education (years)			
Preoperative comorbidity			
Hypertension (n=)			
Coronary heart disease (n=)			
Arrhythmia (n=)			
Hx of cardiac surgery (n=)			
Stroke (n=)			
COPD (n=)			
Diabetes mellitus (n=)			
Liver dysfunction[1] (n=)			
Renal dysfunction[2] (n=)			
Chronic smoking[3] (n=)			
Alcoholism[4] (n=)			
Charlson Comorbidity Index (score)			
Hx of non-cardiac surgery (n=)			
Preoperative medication			
Anticholinergic			
Antidepressant			
Antipsychotic			
Insulin for diabetes mellitus			
Chronic use of benzodiazepine			
Preoperative laboratory tests			
Hematocrit< 30%			
Albumin < 30 g/L			
Glucose < 4.0 or > 10.0 mmol/L			

Sodium < 135.0 or > 145.0 mmol/L			
Potassium< 3.5 or > 5.5 mmol/L			
Dehydration index[5] > 36			
Preoperative ASA classification			
II			
III			

Data are mean (SD) or number (%). BMI = body mass index; COPD = chronic obstructive pulmonary disease; ASA = American Society of Anesthesiologists.
[1]Alanine transaminase and/or aspartate transaminase more than five times the upper limit of normal.
[2]Serum creatinine > 177 μmol/L.
[3]Smoking half a pack of cigarettes per day for at least 2 years.
[4]Two drinks or more weekly, or weekly consumption of the equivalent of 150 ml of alcohol. [5]Dehydration index = [(BUN/3.55)/(Scr/88.4)]x10; BUN = blood urea nitrogen in mmol/L; Scr = serum creatinine in μmol/L.

Section G: Occurrence of non-delirium complications after surgery

	Intervention (n=)	**Control (n=)**	**p value**
Circulatory insufficiency			
Acute myocardial infarction			
New onset arrhythmia			
Pulmonary infection			
Stroke			
Acute renal failure			
Wound dehiscence			
Ileus			
Surgical bleeding			
Anastomotic leakage			
Gastrointestinal hemorrhage			
Wound infection			
Severe sepsis			
Urinary tract infection			

Data are number (%).