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**The effects of subanaesthetic S-ketamine on postoperative delirium and cognitive function in elderly patients undergoing non-cardiac thoracic surgery: a protocol for a randomised, double-blinded, placebo- and positive-controlled, non-inferiority trial**

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Manuscripts

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4 **The effects of subanaesthetic S-ketamine on postoperative delirium and cognitive**  
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6 **function in elderly patients undergoing non-cardiac thoracic surgery: a protocol for**  
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8 **a randomised, double-blinded, placebo- and positive-controlled, non-inferiority trial**

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11 **(SKED Trial)**  
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## Abstract

**Introduction:** Postoperative delirium (POD) is a common and distressing complication after thoracic surgery. S-ketamine has neuroprotective properties as a dissociative anaesthetic. Emerging literature has indicated that S-ketamine can reduce cognitive impairment in patients with depression. However, the role of S-ketamine in preventing postoperative delirium remains unknown. Therefore, this study aims to evaluate the effect of intraoperative prophylactic S-ketamine compared to that of dexmedetomidine on the incidence of postoperative delirium in elderly patients undergoing non-cardiac thoracic surgery.

**Methods and analysis:** This will be a randomised, double-blinded, placebo-controlled, positive-controlled, non-inferiority trial that enrolled patients aged 60 to 90 years undergoing thoracic surgery. The patients will be randomly allocated in a ratio of 1:1:1 to S-ketamine, dexmedetomidine, or normal saline placebo groups using computer-generated randomisation with a block size of six. The primary outcome will be the incidence of postoperative delirium within four days after surgery and this will be assessed using a 3-Minute Diagnostic Confusion Assessment Method (3D-CAM) twice a day. The severity and duration of postoperative delirium, the incidence of emergency delirium, postoperative pain, quality of sleep, cognitive function, and the plasma concentrations of acetylcholine, brain-derived neurotrophic factor, and tumour necrosis factor- $\alpha$  will be evaluated at designated timepoints as secondary outcomes.

**Ethics and dissemination:** Ethical approval has been obtained from the Institutional Review Board of the Cancer Hospital and the Institute of Guangzhou Medical University (ZN202119). At the end of the trial, we commit to making a public disclosure available, regardless the outcomes. The public disclosure will include a publication in an appropriate journal and an oral presentation at academic meetings.

**Trial registration number:** ChiCTR2100052750

**Key words:** Postoperative delirium; S-ketamine; Dexmedetomidine

## Strengths and limitations

- ▶ In this randomised controlled trial, we will evaluate, for the first time, the prophylactic effect of S-ketamine on postoperative delirium in elderly patients undergoing non-cardiac thoracic surgery.
- ▶ Methodology strengths of this non-inferiority study involve placebo- and positive-comparators, concealed assignment, blinded assessment and representative sample size.
- ▶ It is a pragmatic trial that will occur in a real-world setting with standardised anaesthetic management. Moreover, the study team is equipped with a rich experience in postoperative neurocognitive function assessment.
- ▶ This is a single-centre study that exclusively involves thoracic surgery; therefore, the generalisability may not be extrapolated.
- ▶ An anticipated non-inferiority margin ratio of 1.5 in our trial may be too large, and consequently, the sample size may be underestimated.

## Introduction

Postoperative delirium (POD) is a neuropsychiatric disorder in elderly patients, manifested as an acute onset of altered and fluctuating consciousness, inattention, and disorganised thinking, typically during the first 96 hours after surgery. Postoperative delirium reportedly appears in up to 60% of patients, varying with the age and surgical procedure, although its incidence is underestimated since the hypoactive subtype is not well appreciated. [1-3] Postoperative delirium is associated with prolonged hospital stay, long-term cognitive and social dysfunction, and even death. [4-6] The 1-year survival probability is reduced by approximately 10% for each additional day of postoperative delirium. [7] The pathophysiological mechanism of delirium has not been well-elucidated, and neuroinflammation remains a topic of mainstream research interest. Furthermore, its development results from the complicated interaction of multifactorial risks, such as pain, opioids, sleep deprivation, and inflammation, which poses a challenge for the prevention and treatment of postoperative delirium. [8] Although various techniques, including multi-component non-pharmacological interventions, are suggested to reduce the risks, the

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4 status of current evidence has hampered the recommendations on specific prophylactic  
5 agents or doses pragmatically.  
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8 Dexmedetomidine is a highly selective  $\alpha$ -2 adrenergic receptor agonist that is associated  
9 with sedative, sympatholytic, and anti-inflammatory effects, and has the highest-ranking  
10 possibility of preventing postoperative delirium. [6] Furthermore, the plausibility of  
11 dexmedetomidine's positive effects on postoperative delirium is enhanced by evidence of  
12 less anticholinergic activity and opioid-sparing properties. [9] Postoperative prophylactic  
13 low-dose dexmedetomidine could remarkably reduce the incidence of delirium during  
14 seven days after non-cardiac surgery; [10] moreover, perioperative infusion of  
15 dexmedetomidine halved the incidence of delirium in the elderly after major cardiac and  
16 non-cardiac surgery without the increase in adverse effects. [11,12] A meta-analysis of  
17 1301 patients undergoing cardiac surgery revealed that dexmedetomidine decreased  
18 postoperative delirium. [13] Nevertheless, this meta-analysis should be interpreted with  
19 caution, because several of the included studies did not consider delirium as the primary  
20 outcome, the methodology of delirium assessment varied, and dexmedetomidine  
21 administration was also inconsistent, with differing doses and durations. Furthermore, the  
22 finding that dexmedetomidine prevents postoperative delirium is also controversial. In the  
23 DECADE trial, continuous infusions of dexmedetomidine, commenced at induction and  
24 maintained for 24 hours, failed to reduce delirium in patients recovering from cardiac  
25 surgery. Notably, dexmedetomidine non-significantly aggravated delirium, probably  
26 mediated by hypotension. [14] A randomised controlled trial found that intraoperative  
27 dexmedetomidine did not decrease postoperative delirium or affect cognitive function in  
28 the elderly undergoing major non-cardiac surgery. [15] As with all pharmacological  
29 treatment options, the side effects of dexmedetomidine are bradycardia and hypotension  
30 in a dose-dependent manner, and more strikingly in the elderly; hence, close  
31 haemodynamic monitoring is warranted.  
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55 Ketamine, a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist, is  
56 pharmacologically rationalised as an effective medication for reducing postoperative  
57 delirium, probably due to its neuroprotective properties. Under surgical conditions, the  
58 enhanced AMPA/NMDA signalling caused by the activation of cytokine receptors, and high  
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4 mobility group box 1 facilitate an increased influx of glutamate in hippocampal neurones,  
5 which ultimately promotes glutamate toxicity. [16] Ketamine can mitigate neuronal  
6 apoptosis by inhibiting the activation of NMDA receptors and the transduction of excitatory  
7 signals. [17] The assumption of ketamine's beneficial effects on delirium is also  
8 strengthened by evidence of its opioid-sparing and antidepressant effects. Depression and  
9 delirium, induced by similar pathophysiological mechanisms, are thought to overlap. [18,19]  
10 A small sample size of a randomised controlled trial indicated that a low-dose single bolus  
11 of ketamine at induction significantly attenuated delirium after cardiac surgery. However,  
12 the PODCAST study showed that low-dose ketamine failed to decrease postoperative  
13 delirium, pain, and opioid consumption, and generated a dose-dependent increase in the  
14 occurrence of negative experiences. [20] The PRIDe study offered no possibility for  
15 ketamine to prevent postoperative cognitive decline, including delirium. [21]

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27 S-ketamine, an enantiomer of ketamine, possesses greater pharmacological potency  
28 and fewer psychotomimetic side effects. Animal experiments showed that S-ketamine,  
29 rather than racemic ketamine, could alleviate the injury of hippocampal neurones exposed  
30 to glutamate in rodents; a subanaesthetic dose of S-ketamine could remarkably mitigate  
31 neuroinflammation by inhibiting microglia proliferation and TLR4/NF- $\kappa$ B signalling pathway  
32 activation, which consequently improved neurocognitive function. [22,23] Additionally, S-  
33 ketamine could promote the plasticity of hippocampal neurones and improve the function  
34 of neurones in the prefrontal and hippocampal neural circuits. [24] A study on healthy  
35 volunteers showed that S-ketamine exhibited pro-neuroplastic effects on hippocampal  
36 structure, which may improve cognitive function after surgery. [25] Moreover, a recent  
37 study on human metabolome revealed that S-ketamine could inhibit brain uptake of  
38 aromatic amino acid, such as tryptophan and tyrosine, to increase the plasma level of  
39 serotonin and noradrenaline, both of which contributed to the improvement of depression  
40 and cognitive impairment. [26] Besides, the sympathomimetic properties of S-ketamine,  
41 which lacks profound haemodynamic depression in the elderly, as well as its analgesic  
42 effect, might explain its non-inferior property for delirium prevention compared to  
43 dexmedetomidine in the elderly. However, S-ketamine is out of favour in the anaesthesia  
44 community probably due to its potential psychiatric side effects and negative results from  
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the PODCAST and PRIDe studies. At present, scarce evidence is available on the prophylactic effect of S-ketamine administration on postoperative delirium.

Since the effects of S-ketamine on postoperative delirium are far from revealed, we designed the current prospective, randomised, double-blinded, placebo- and positive-controlled, non-inferiority trial to investigate the effect of intraoperative prophylactic S-ketamine on postoperative delirium in elderly patients undergoing thoracic surgery compared with dexmedetomidine.

**Methods**

**Study setting and design**

This study will be conducted at the Cancer Hospital and Institute of Guangzhou Medical University (Guangzhou, Guangdong, China, with principal investigator [PI] Dr Yonghua Yao). The study activities are expected to commence in March 2022 and be completed in December 2023. The study design is in accordance with the standard protocol items for randomised trials guidelines. The overall schedule is illustrated in Table 1, and the Consolidated Standards of Reporting Trials flow diagram is shown in Figure 1. The current study protocol is the fifth version.

Table 1. Schedule of enrolment, interventions, and assessments for the trial

	Enrolment	Allocation	Post-allocation									Closeout
	Preoperative assessment	Allocation	Before induction	recovery	4-hour after surgery	24-hour after surgery	48-hour after surgery	72-hour after surgery	96-hour after surgery	30-day after surgery	60-day after surgery	
TIME POINT	-T <sub>1</sub>	T <sub>0</sub>	T <sub>1</sub>	T <sub>2</sub>	F <sub>1</sub>	F <sub>2</sub>	F <sub>3</sub>	F <sub>4</sub>	F <sub>5</sub>	F <sub>6</sub>	F <sub>7</sub>	
<b>ENROLMENT:</b>												
Eligibility screen	X											
Informed consent	X											
Allocation		X										
<b>INTERVENTIONS:</b>												
S-ketamine			←→									
Dexmedetomidine			←→									
Normal Saline			←→									
<b>ASSESSMENTS:</b>												
Postoperative delirium (3D-CAM)					X	X	X	X	X			
Pain severity (NRS)					X	X	X					



Sleep quality (NRS)						x	x	x	x		
Cognitive function (TICS-40)										x	x
Haemodynamic variables			←————→								
Emergency delirium (RASS)				x							
Plasma biomarkers (ACh, BDNF, TNF- $\alpha$ )			x	x					x		

## Participant recruitment

### Inclusion criteria

1. Aged 60 to 90 years old.
2. Both sexes.
3. American anaesthesiologist association (ASA) physical status classification I-III.
4. Diagnosed with pulmonary, oesophageal or mediastinal disorders.
5. Undergoing open or video-assisted thoracic surgery, including lobectomy, segmentectomy, pneumonectomy, oesophagectomy, or resection of the mediastinal tumour.
6. General anaesthesia with one lung ventilation (OLV) or bronchial blocker.
7. An expected operation duration of 2 hours or more.
8. Voluntary participation in the trial and signed informed consent.

### Exclusion criteria

1. History of psychiatric disease or severe depression.
2. History of glaucoma or hyperthyroidism.
3. History of severe hepatic (Child-Pugh grade C) or renal (requirement for renal replacement therapy) disorders.
4. Body mass index (BMI) > 35 kg/m<sup>2</sup>.
5. Dementia history or baseline Mini-Mental State Examination (MMSE) score of < 23.
6. Severe audio-visual impairments, or inability to speak Mandarin or Cantonese precluding communication.
7. Sinus bradycardia (heart rate < 50 beats per minute, bpm), sick sinus or Wolff-Parkinson-White syndrome, or 2nd degree atrioventricular block and over.

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- 4 8. Uncontrolled hypertension (baseline value > 200/110 mm Hg).
- 5
- 6 9. Allergic to dexmedetomidine or S-ketamine.
- 7
- 8 10. Taking sedatives, antidepressants or glucocorticoids.
- 9
- 10 11. Alcohol or drug abuser.
- 11
- 12 12. Life expectancy of less than two months due to extensive tumour metastasis.
- 13
- 14

### 15 **Participants consent**

16 All patients scheduled for thoracic surgery will be screened one day before the operation  
17 for eligibility at the preoperative evaluation clinic (or on Friday for those who will undergo  
18 surgery the following Monday). Eligible patients will be informed by the study team  
19 coordinator. For the sake of voluntary participation, all patients will be informed about the  
20 aims, procedures, benefits, possible risks of study, and how to react if risks occur. If  
21 interested in enrolment, the patients or their next of kin will sign the written consent form  
22 in triplicate.  
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### 33 **Randomisation and blindness**

34 A randomisation code will be generated in a block size of six on the website of  
35 <http://www.Randomization.com> and kept in a sealed opaque envelope by an anaesthetist  
36 nurse. The patients will be randomly allocated by a ratio of 1:1:1 to the S-ketamine group  
37 (S group), dexmedetomidine group (D group), or control group (C group) by an anaesthetist  
38 nurse. Dispensing and labelling of the study drugs will be performed by a pharmacist. Both  
39 the anaesthetist nurse and the pharmacist will not be involved in the following research or  
40 follow-up. The randomisation protocol will be kept secure by the primary investigator.  
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48 The labelled "Study medication" syringes (50 ml), identical in appearance, and the  
49 infusion regimen formulated by the pharmacist based on the randomisation, will be  
50 distributed to the attending anaesthesiologists responsible for anaesthetic management as  
51 soon as the research team informs the central pharmacy about the patient heading for  
52 surgery. In order to avoid anaesthesiologists' speculation about the randomised  
53 assignment, the study drugs will be infused at a similar rate (see Table 2). The  
54 anaesthesiologists, patients, investigators responsible for follow-up, and statisticians will  
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4 be all blinded to the randomised allocations until the final statistical analyses are completed.  
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6 The blindness will be unmasked by the primary investigator in a medical emergency,  
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8 including deterioration of the patient's condition intraoperatively or adverse events  
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10 postoperatively.  
11  
12

### 13 **Standard anaesthetic management**

14  
15 On the day of the operation, the patients will be admitted to the operating room after  
16  
17 random assignment. Vital signs will be routinely monitored, including heart rate (HR), blood  
18  
19 pressure (BP), oxyhaemoglobin saturation by pulse oximetry (SpO<sub>2</sub>), end-tidal carbon  
20  
21 dioxide partial pressure (EtCO<sub>2</sub>), nasopharyngeal temperature, and urine output  
22  
23 throughout surgery. Pre-oxygenation with 100% oxygen for 15 min before the induction of  
24  
25 anaesthesia will be delivered to the patient using a face mask. Atropine will be  
26  
27 administered intravenously in avoidance of excessive secretions.  
28

29  
30 After A-line and V-line are cannulated under ultrasound guidance, anaesthesia induction  
31  
32 will be performed by sequence administration of midazolam (0.05 mg/kg), propofol (1-2  
33  
34 mg/kg) or etomidate (0.2 mg/kg), and sufentanil (0.2-0.4 µg/kg). After the patient becomes  
35  
36 unconscious, rocuronium (0.9 mg/kg) will be injected intravenously. Bronchial intubation  
37  
38 will be performed smoothly with a video laryngoscope after 3-minute positive pressure  
39  
40 ventilation. The tip of double lumen tubes (DLTs) will be inserted into the glottis under direct  
41  
42 vision and advanced until a mild resistance is perceived. After the fiberoptic bronchoscope  
43  
44 is fully lubricated, it will be advanced into the tracheal lumen of the DLTs until the carina is  
45  
46 identified. Afterwards, the ideal position of the bronchial lumen (the blue bronchial cuff  
47  
48 should be invisible for left DLTs, the opening in the upper lobe of the right lung should be  
49  
50 visible for right DLTs) will be verified. Dual-controlled ventilator modes (i.e. pressure-  
51  
52 controlled ventilation with volume guaranteed or pressure-regulated volume control) will  
53  
54 be applied. One-lung protective ventilation regimen will be conducted by a combination of  
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56 tidal volumes (Vt) of 6 ml/kg or lower, by predicted body weight, with a positive end-  
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58 expiratory pressure of 6 cmH<sub>2</sub>O or beyond based upon guidelines and expert opinion for  
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60 optimal practice during OLV. [27] High inspiratory fractions of oxygen (FiO<sub>2</sub> > 70%) will be  
administered to maintain SpO<sub>2</sub> higher than 94%. In addition, continuous positive airway

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4 pressure (CPAP) regimen will be considered when necessary. The respiratory rate will be  
5  
6 adjusted to maintain EtCO<sub>2</sub> at 35-45 mmHg. Sedative maintenance will be performed with  
7  
8 a TCI (target-controlled infusion) of propofol according to the Schnider model at a plasma  
9  
10 concentration (Cp) of 2-3 µg/ml to maintain the bispectral index value between 40 and 60.  
11  
12 Analgesic maintenance will be achieved with a TCI of remifentanyl according to the Minto  
13  
14 model at a Cp of 1-6 ng/ml to fluctuate the HR and BP within the baseline value ± 20%. An  
15  
16 intermittent bolus of rocuronium will be administered to maintain TOF < 1 intraoperatively.  
17  
18 Forced air-warm blankets will be used to ensure an intraoperative body temperature of 36-  
19  
20 37°C. The surgeon will implement an intercostal nerve block (T3-7) with 20 ml of 0.5%  
21  
22 ropivacaine under direct thoracoscopic view before placing a chest tube. The sign of a  
23  
24 successful block is the presence of pleural displacement. All participants will be given  
25  
26 hydromorphone (0.015 mg/kg) when a chest tube is placed for the sake of prophylaxis of  
27  
28 hyperalgesia.

29  
30 A patient-controlled analgesia (PCA) device, with hydromorphone (0.15 mg/kg) and  
31  
32 ondansetron (12 mg) in a total volume of 100 ml, will be connected to the intravenous  
33  
34 cannula at the end of surgery. The device is programmed to administer a background dose  
35  
36 of 2 ml/h, as well as a bolus dose of 0.5 ml with a lockout interval of 15 min for 48 hours.  
37  
38 Hydromorphone (0.008 mg/kg) will be administered if the numeric rating scale (NRS) score  
39  
40 is > 5 despite the PCA regimen. Residual neuromuscular blockade will be routinely  
41  
42 reversed with neostigmine (40 µg/kg) and atropine (20 µg/kg), and the endotracheal tube  
43  
44 will be removed when the patients are able to follow verbal commands.

### 45 46 **Study drugs administration**

47  
48 S-ketamine (50 mg, 2 ml) is diluted to 50 ml (1 mg/ml) with 48 ml normal saline;  
49  
50 dexmedetomidine (200 µg, 2 ml) is diluted to 100 ml (2 µg/ml) with 98 ml normal saline;  
51  
52 the control group only receives 50 ml normal saline in light of blindness. All drugs are  
53  
54 identical in appearance, packaged in identical 50 ml syringes labelled with "Study  
55  
56 medications". The loading dose of study drugs will be infused within 10 minutes before  
57  
58 induction, and the maintenance dose will be infused at a constant rate continuously until  
59  
60 skin closure. The administrative protocol of study drugs is shown in Table 2.

**Table 2 Study drugs and administrative protocol (take a 60 kg patient as an example)**

Group	Concentration	Loading dose	Maintenance dose
S-ketamine	1 mg/ml	0.25 mg/kg	0.1 mg/kg/h
i.e. The administrative protocol of a 60 kg patient will be a loading dose of 15 ml and a maintenance dose of 6ml/h			
Dexmedetomidine	2 $\mu$ g/ml	0.4 $\mu$ g/kg	0.2 $\mu$ g/kg/h
i.e. The administrative protocol of a 60 kg patient will be a loading dose of 12 ml and a maintenance dose of 6 ml/h			
Control	Normal saline	S or D	S or D
i.e. The administrative protocol of a 60 kg patient will refer to either S or D group			

**Data collection**

The following data will be collected through patient interviews and abstractions from the electronic medical record system:

**Preoperative data collection**

1. Patient demographic data including age (years), sex, height (cm), weight (kg), BMI ( $\text{kg}/\text{m}^2$ ), and education level (years).
2. ASA classification, Charlson comorbidity index, baseline MMSE, and type of surgery.
3. Plasma biomarker concentrations including acetylcholine (ACh), brain-derived neurotrophic factor (BDNF) and tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ) before the administration of study drugs (T1).

**Intraoperative data collection**

1. Haemodynamic parameters including HR (bpm), mean arterial pressure (MAP, mmHg), and SpO<sub>2</sub> at 15-minute intervals.
2. Hypotension and bradycardia episodes (see Table 3).
3. Hypertension and tachycardia episodes (see Table 3).
4. Duration of desaturation (SpO<sub>2</sub> < 94%, minutes).
5. The cumulative dosage of noradrenaline ( $\mu$ g) and atropine (mg).

6. The consumption of propofol (mg) and opioids (converted to morphine milligram equivalent by Global RPH, MME).
7. Surgery, anaesthesia and OLV duration (minutes).
8. Time to extubation (minutes, duration from discontinuation of propofol to removal of the tracheal tube).
9. Emergency agitation (Richmond Agitation-Sedation Scale, RASS score  $\geq$  1).
10. Plasma biomarker concentrations at the end of operation (T2).

### **Postoperative data collection**

1. Incident postoperative delirium at 4 h after surgery and twice daily from postoperative day 1 to postoperative day 4 (8:00-10:00 am) with an interval of at least 6 hours.
2. Severity and duration of delirium.
3. Postoperative pain at 4 h, 1 and 2 days after surgery.
4. Consumption of hydromorphone (mg).
5. Quality of sleep within 4 days after surgery.
6. Cognitive function at 30 and 60 days after surgery.
7. Plasma biomarker concentrations at the 4<sup>th</sup> day after surgery (T3).

Paper case report forms (CRF) will be stored by the primary investigator and entered into the Epidata V4.6 database protected by password only accessible to authorised users. Data will be exported from Epidata to a statistical package in a safe environment for analysis.

### **Outcomes**

#### **Primary outcomes**

The primary outcome will be the incidence of postoperative delirium as defined by any positive assessment at 4 h after surgery and the following 4 days.

#### **Secondary outcomes**

The main secondary outcome will be the subtype, severity and duration of postoperative delirium.

Other prespecified secondary outcomes will be the incidence of emergency delirium; pain

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3 severity at 4 h, 1 and 2 days after surgery; quality of sleep within 4 days after surgery;  
4  
5 cognitive function at 30 and 60 days after surgery; plasma biomarker (ACh, BDNF, TNF-  
6  
7  $\alpha$ )  
8  
9 concentrations at T1-3; and incidence of adverse events.  
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### 13 **Measurement of outcomes**

#### 14 **Measurement of delirium**

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17 Delirium will be assessed using a validated 3-minute diagnostic confusion assessment  
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19 method (3D-CAM, with a sensitivity of 84%–99% and specificity of 90%–97%) [28] or  
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21 Confusion Assessment Method for the Intensive Care Unit (CAM-ICU), for patients who  
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23 have a tracheal tube or underwent tracheostomy. [29] 3D-CAM resolves the four diagnostic  
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25 features of delirium: (1) acute onset and fluctuating course, (2) inattention, (3) disorganised  
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27 thinking, and (4) altered level of consciousness. A patient who displays both features 1 and  
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29 2, with either feature 3 or 4, will be diagnosed with delirium (see Figure 2). [28] Delirium  
30  
31 assessments will be performed only when patients can be aroused sufficiently with an  
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33 RASS score of -3 to 4 (Supplementary Table 1). Patients with postoperative delirium will  
34  
35 be classified into three subtypes. Hyperactive delirium will be defined when the RASS  
36  
37 score ranges from 1 to 4; hypoactive delirium will be defined when the RASS score ranges  
38  
39 from -1 to -3, and mixed delirium will be defined when the RASS score ranges from 1 to 4  
40  
41 and -1 to -3 alternatively. The severity of postoperative delirium will be rated using the  
42  
43 CAM-Severity short-form scale (Supplementary Table 2). Mild-to-moderate delirium will be  
44  
45 defined as a CAM-S score of 3 to 5, while severe delirium will be defined as a CAM-S score  
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47 of 6 to 7. [30]

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49 Two investigators who are not involved in perioperative care will be responsible for  
50  
51 postoperative delirium assessments and will be trained by a psychiatrist with regard to  
52  
53 symptoms, diagnosis, and treatment of delirium. Furthermore, the psychiatrist will explain  
54  
55 the protocols of 3D-CAM and CAM-ICU in detail, and will perform the simulation training of  
56  
57 delirium assessment until a kappa value over 0.8 is achieved between investigators and  
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59 psychiatrists. The training process will be repeated every 4-6 months throughout the study.  
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In addition, the chart-based delirium identification instrument with the information primarily

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4 derived from electronic medical records system and recalling descriptions of caregivers  
5 will be employed to detect any cases of delirium in patients that may occur outside of in-  
6 person delirium assessments (Supplementary Table 3). [31]  
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### 9 **Pain and sleep quality measurement**

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11 Postoperative pain at rest and during a cough will be evaluated using an 11-point NRS (0  
12 = [no pain], 0 < NRS < 4 [mild pain], 4 ≤ NRS < 7 [moderate pain], 7 ≤ NRS < 10 [severe  
13 pain], NRS = 10 [worst pain imaginable]). Postoperative sleep quality will also be evaluated  
14 using the NRS (0 = best-quality sleep, 10 = worst-quality sleep).  
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### 19 **Cognitive function measurement**

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21 Postoperative cognitive function will be assessed using the Chinese version of the  
22 Telephone Interview for Cognitive Status-40 (TICS-40). The TICS-40 scale used in this  
23 study consists of nine items with a maximum score of 40 points, including the following  
24 variables and corresponding points: address (3 points), current date (5 points), counting  
25 backwards (2 points), word-list recalling (10 points), subtractions (5 points), object naming  
26 (2 points), repetition (1 point), the president and prime minister's names (2 points), and  
27 delayed recall of the word list (10 points). A score below 21 will be defined as mild cognitive  
28 impairment (Supplementary Table 4). [32]  
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### 36 **Biomarkers concentration measurement**

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38 Venous blood (approximately 6 ml) will be sampled and stored on ice in vacutainer tubes  
39 containing EDTA. Within 30 min, the samples will be centrifuged at 4°C for 20 min at 2000×  
40 g to obtain plasma and then stored at -80°C. We will measure ACh, BDNF, and TNF-α  
41 levels by enzyme-linked immunosorbent assay method (in accordance to manufacturer's  
42 instructions).  
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### 50 **Adverse events**

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52 An adverse event (AE) can be any unfavourable and unintended symptom or side effect  
53 temporally associated with the use of study medications. The potential AEs that may be  
54 considered in this trial are bradycardia, hypotension, tachycardia, hypertension, arrhythmia,  
55 nystagmus, hypersalivation, euphoria, emergency agitation, hallucinations, and  
56 nightmares. It is possible, but very unlikely, that low-dose S-ketamine (50 mg in total)  
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administered intraoperatively will cause these psychiatric effects. Potential adverse events and medical rescue are shown in Table 3. [33]

Serious AEs are rare, life-threatening events that may be associated with the study drugs or perioperative incidents, such as death or serious cardio-cerebral vascular events.

**Table 3 The definitions of adverse events and corresponding medication rescue**

Adverse events	Severity	Definition	Treatment
Hypotension (SBP<90 mm Hg or DBP<50 mm Hg or MAP<80% baseline)	Mild	SBP 80-89 mm Hg	Close monitoring
	Moderate	SBP 70-79 mm Hg>2 min	Noradrenaline 4 $\mu$ g
	Severe	SBP 60-69 mm Hg>1 min	Noradrenaline 8 $\mu$ g
	Life-threatening	SBP 60-69 mm Hg and unresponsive to noradrenaline or SBP<60 mm Hg	Intensive intervention and suspend the study
Hypertension (SBP>140 mm Hg or DBP>90 mm Hg or MAP>120% baseline)	Mild	SBP 141-160 mm Hg or DBP 91-100 mm Hg	Close monitoring
	Moderate	SBP 160-170 mm Hg or DBP 101-110 mm Hg	Urapidil 12.5 mg
	Severe	SBP 171-180 mm Hg or DBP 111-120 mm Hg >3 min	Urapidil 25 mg or NG 50 $\mu$ g
	Life-threatening	SBP >180 mm Hg or DBP >120 mm Hg and unresponsive to NG >2 min	Intensive intervention and suspend the study
Bradycardia (HR<60 bpm)	Mild	HR 55-60 bpm	Close monitoring
	Moderate	HR 50-54 bpm>3 min	Atropine 0.5 mg
	Severe	HR 40-50 bpm>2 min	Atropine 1.0mg
	Life-threatening	HR<40 bpm and unresponsive to atropine	Intensive intervention and suspend the study
Tachycardia (HR>100 bpm)	Mild	HR 90-100 bpm	Close monitoring
	Moderate	HR 101-110 bpm>3 min	Esmolol 20 mg
	Severe	HR 111-130 bpm>2 min	Atropine 40 mg
	Life-threatening	HR>130 bpm and unresponsive to Esmolol	Intensive intervention and suspend the study
Hypoxemia (SpO <sub>2</sub> <94%)	Mild	SpO <sub>2</sub> 90%-94%	Close monitoring
	Moderate	SpO <sub>2</sub> 80%-90%>3 min	CPAP
	Severe	SpO <sub>2</sub> 70%-79%>2 min	Two-lung ventilation
	Life-threatening	SpO <sub>2</sub> <70% and unresponsive to two-lung ventilation	Intensive intervention and suspend the study

Emergency delirium	Mild	RASS 1-2	Limb restraint
	Severe	RASS 3-4	Propofol 30 mg
Hallucination/Nystagmus	NA	3D-CAM	Haloperidol 10 mg

3D-CAM, 3 minutes diagnostic confusion assessment method; CPAP, constant positive airway pressure; HR, heart rate; NA, not applicable; NG, nitro-glycerine; RASS, Richmond Agitation-Sedation Scale.

### Sample size calculation

The sample size was calculated for the main outcome, the incidence of postoperative delirium, using PASS software version 11.0. Based on previous studies and our recently completed data, we estimated that the incidence of POD in elderly patients undergoing non-cardiac thoracic surgery was 40%. [8,34-38] Assuming that dexmedetomidine is associated with a 40% relative reduction in the incidence of postoperative delirium, the non-inferiority margin rate ratio (RR) of S-ketamine versus dexmedetomidine will be set at 1.5. [10,21,39,40] To achieve a two-sided type I error of 5% and 80% power, 729 participants (243 patients per arm) will be recruited. To accommodate a 5% dropout rate, the final sample size will be 780 (260 patients per arm).

### Statistical methods

Kolmogorov-Smirnov test will be used to evaluate the normal distribution of continuous variables. Normally distributed data will be presented as means  $\pm$  standard deviation (SD), and non-normally distributed data will be presented as medians with interquartile ranges. Categorical data will be summarised as counts (proportions).

The absolute standardised difference (ASD) will be used for the comparison of baseline data among the three groups, that is, the absolute difference in means, mean ranks, or proportions divided by the combined SD. Baseline variables with  $ASD > 0.013$  (i.e.,  $1.96 \times \sqrt{(260 + 260 + 260)/(260 \times 260 \times 260)}$ ) are considered to be imbalanced and will be adjusted for in all analyses when necessary.

For the primary outcome, the incidence of postoperative delirium, the intention-to-treat approach and per-protocol (PP) approach will be performed. Pearson's chi-square test will

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4 be applied to compare proportions with the primary outcome among groups. The difference  
5 among groups will be expressed as RR and 95% confidence interval (CI), while non-  
6 inferiority will be identified if the upper limit of 95% CI of RR is  $< 1.5$ . For the secondary  
7 outcomes, only the PP approach will be used. Normally distributed data will be analysed  
8 with one-way analysis of variance (ANOVA); Non-normally distributed data will be  
9 analysed with Kruskal-Wallis test. The median difference will be calculated using the  
10 Hodges-Lehmann estimation on the basis of the Kruskal-Wallis test. Adverse events that  
11 are presented as incidences will be compared by calculating the 95% CI of the incidence  
12 difference: incidence (S group) – incidence (D group), and noninferiority will be achieved  
13 if the upper limit of 95% CI is  $< 5\%$ . The superiority for outcomes will be assessed when  
14 noninferiority is verified.

15  
16 To account for correlation among repeated measurements, such as numeric rating  
17 scores for pain and sleep quality, plasma biomarker concentrations, and cognitive function,  
18 will be compared using generalised estimating equation analysis among groups. The time  
19 to delirium will be calculated with the Kaplan-Meier estimator, and the differences among  
20 groups will be assessed by the log-rank test. The number needed to treat will be estimated  
21 for the primary outcome.

22  
23 Missing values will be adjusted using random forest imputation in the missForest  
24 package. However, missing values, due to fatigue in the assessment or the patient's  
25 inability to cooperate, will be imputed with positive results or means in the corresponding  
26 treatment group and time point. If the patient did not have a delirium assessment at all (e.g.  
27 dropout or death), no values will be imputed. The last assessment is used to replace the  
28 missing value to estimate the incidence of postoperative delirium in patients who are  
29 discharged or die within 4 days, while the missing value of assessment per day does not  
30 need to be replaced.

31  
32 The *P* values and CIs reported from one-way ANOVA and Kruskal-Wallis test will be  
33 considered to illustrate statistical significance if they are less than 0.017 and 98.3%,  
34 respectively, accounting for three pairwise comparisons. The family-wise significance and  
35 CI levels among the three groups will be set at 0.05% and 95%, respectively. For the pain  
36 intensity score, a 1.1 decrease will be considered the minimal clinically important difference.

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5 Analyses will be conducted using IBM SPSS version 25.0 (SPSS Software, Chicago,  
6 IL, USA), R statistics version 4.1.2 (R Project for Statistical Computing), and GraphPad  
7 Prism version 8.0 (GraphPad Software, San Diego, CA, USA).  
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### 13 **Ethics and confidentiality**

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15 Ethical approval was obtained from the Institutional Review Board of the Cancer Hospital  
16 and the Institute of Guangzhou Medical University (ZN202119). The study has also been  
17 registered at Chictr.org.cn with the identifier ChiCTR2100052750. The personal  
18 information of the participants will not be disclosed unless authorisation is approved. In  
19 addition, each participant will be provided with a unique identity code, the information of  
20 which will be properly secured. The CRF and Epidata database will be retained for a  
21 minimum of 10 years.  
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### 31 **Patient and Public Involvement**

32 No patients or public representatives were involved in the design of this trial.  
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### 36 **Dissemination**

37  
38 At the end of the trial, we commit to making public disclosure available despite the outcome.  
39 Public disclosure will include publication in an appropriate journal or oral presentation at  
40 an academic meeting. The PI will be considered the first or corresponding author. The  
41 investigators who contribute a minimum of four months to the trial will be co-authors;  
42 otherwise, they will be acknowledged in the publication.  
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### 50 **Discussion**

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52 Lung cancer ranks first among all malignancies in China, and anatomic pulmonary  
53 resection is a major component of multimodal therapy according to the lung cancer  
54 guidelines. [8] However, more than 40% of patients undergoing lung cancer surgery are  
55 inflicted by severe depression-related psychological suffering postoperatively. [42]  
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57 Depression is an independent predictor of postoperative delirium in patients who undergo  
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4 miserable orthopaedic and cancer surgeries. [18] Based on its pharmacological  
5 mechanisms and antidepressant effects, we speculate that S-ketamine would be non-  
6 inferior to dexmedetomidine in reducing postoperative delirium to some extent in the elderly,  
7 with fewer episodes of hypotension or less opioid consumption. Hypotension is pertinent  
8 to delirium, and minimisation of intraoperative hypotension episodes is recommended to  
9 reduce postoperative delirium. [43] Additionally, the administration of opioids (long-acting  
10 opioids in particular) is closely related to postoperative delirium in a dose-dependent  
11 manner. Hence, it is critical to abate opioid consumption in order to curtail delirium. [8]  
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19 Although previous studies have demonstrated that ketamine failed to reduce the  
20 incidence of postoperative delirium in patients undergoing major cardiac or non-cardiac  
21 surgery, we will deploy a different administrative protocol to evaluate the effect of an isomer  
22 of ketamine on postoperative delirium accompanied by dexmedetomidine as a positive  
23 comparator and by an optimal sample size. Dexmedetomidine is a highly recommended  
24 agent in the prevention and treatment of postoperative delirium; however, it is commonly  
25 accompanied by hypotension and bradycardia in the elderly. As the prevention of  
26 postoperative delirium is more practical and effective than the treatment itself, creating a  
27 means of prevention for delirium is extraordinarily indispensable. We believe that the  
28 results will be as follows: (1) S-ketamine will be non-inferior to dexmedetomidine in the  
29 prevention of postoperative delirium; meanwhile, more stable haemodynamics, lower  
30 postoperative pain severity, or other beneficial secondary outcomes will be observed with  
31 S-ketamine intervention. Side effects will be compared between groups, all of which will  
32 be our desirables. This suggests that S-ketamine will be an optimal choice for limiting  
33 delirium emergence in the elderly, and further studies should be performed to evaluate its  
34 effect on long-term cognitive function. (2) S-ketamine will be non-inferior to  
35 dexmedetomidine in postoperative delirium prevention with comparable secondary  
36 outcomes; however, it will be accompanied by frequent side effects. This indicates that S-  
37 ketamine will be clinically valueless for delirium prevention, which is also possible in view  
38 of the results from previous studies on ketamine (PODCAST and PRIDe study). (3) S-  
39 ketamine will be inferior to dexmedetomidine in the prevention of postoperative delirium,  
40 which is probably because dexmedetomidine is recognised as the most effective  
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3 medication for delirium, and fewer studies have compared the two drugs. (4) S-ketamine  
4 will be more effective than dexmedetomidine in preventing postoperative delirium. If this is  
5 the case, additional studies would be necessary to elucidate its optimal dosage when  
6 safety is taken into consideration.  
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13 **Authors' contributions** Wei Wei, Anyu Zhang, Xi Zheng, Ming Zhou, and Yonghua Yao  
14 participated in the study design. Wei Wei, Anyu Zhang, and Xi Zheng co-drafted the  
15 protocol manuscript. Yu Gu and Yonghua Yao contributed to sample size calculation and  
16 statistical consultation. Wei Wei and Xi Zheng developed the case report forms and the  
17 Epidata database. Wei Wei, Lv Liu, and Chunlin Tang conducted the preliminary trial.  
18 Yonghua Yao served as the primary investigator and provided the funding. All authors  
19 completed 3D-CAM and CAM-ICU training courses and obtained good clinical practice  
20 certificates.  
21  
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23  
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29  
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40 **Patient consent for publication:** Consent obtained directly from patients.  
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## Figure legends

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4 **Figure 1.** Consolidated Standards of Reporting Trials (CONSORT) flow diagram.

5 **Figure 2.** Overview of 3-minute Diagnostic Confusion Assessment Method (3D-CAM)  
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7 assessment.

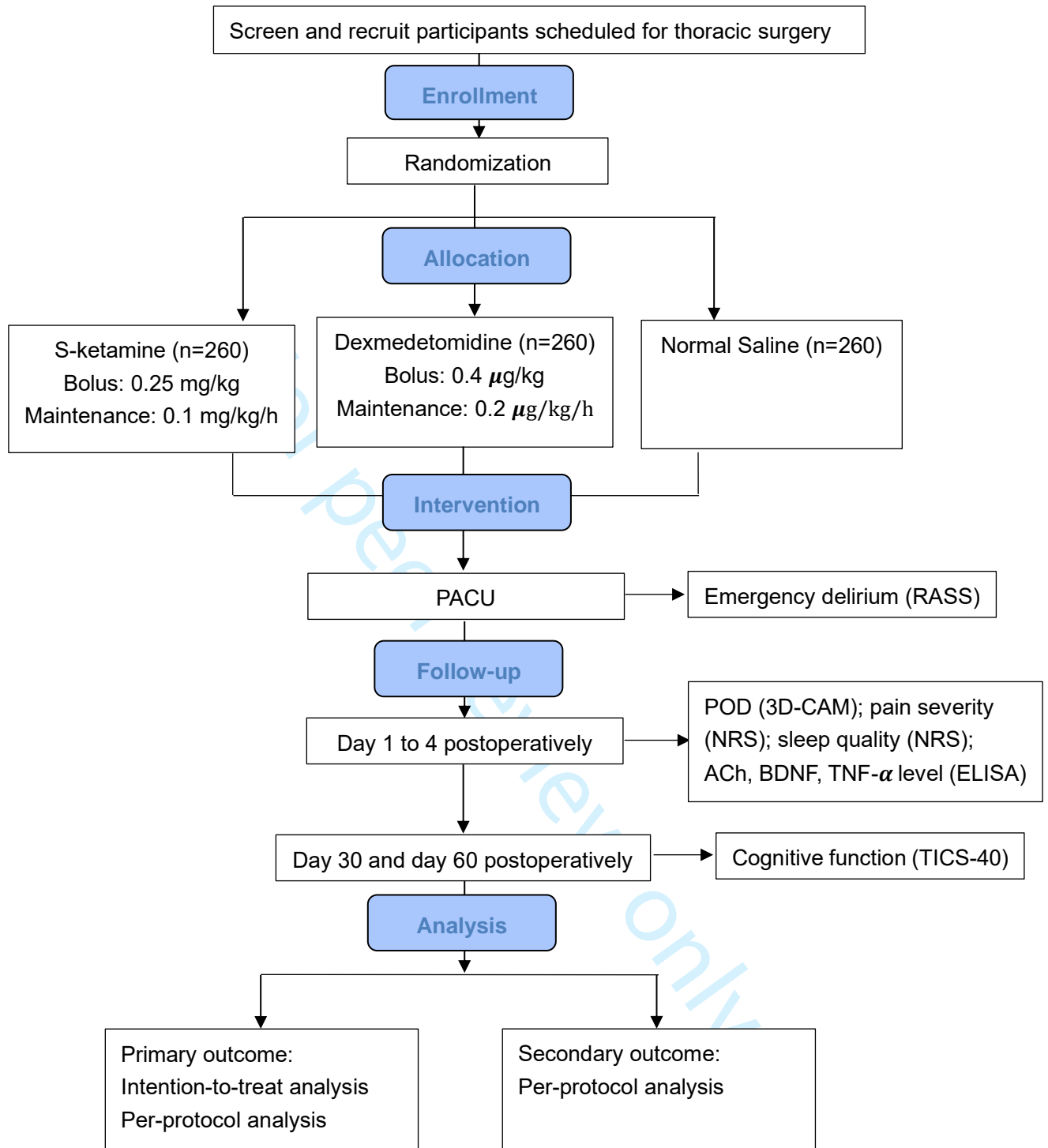
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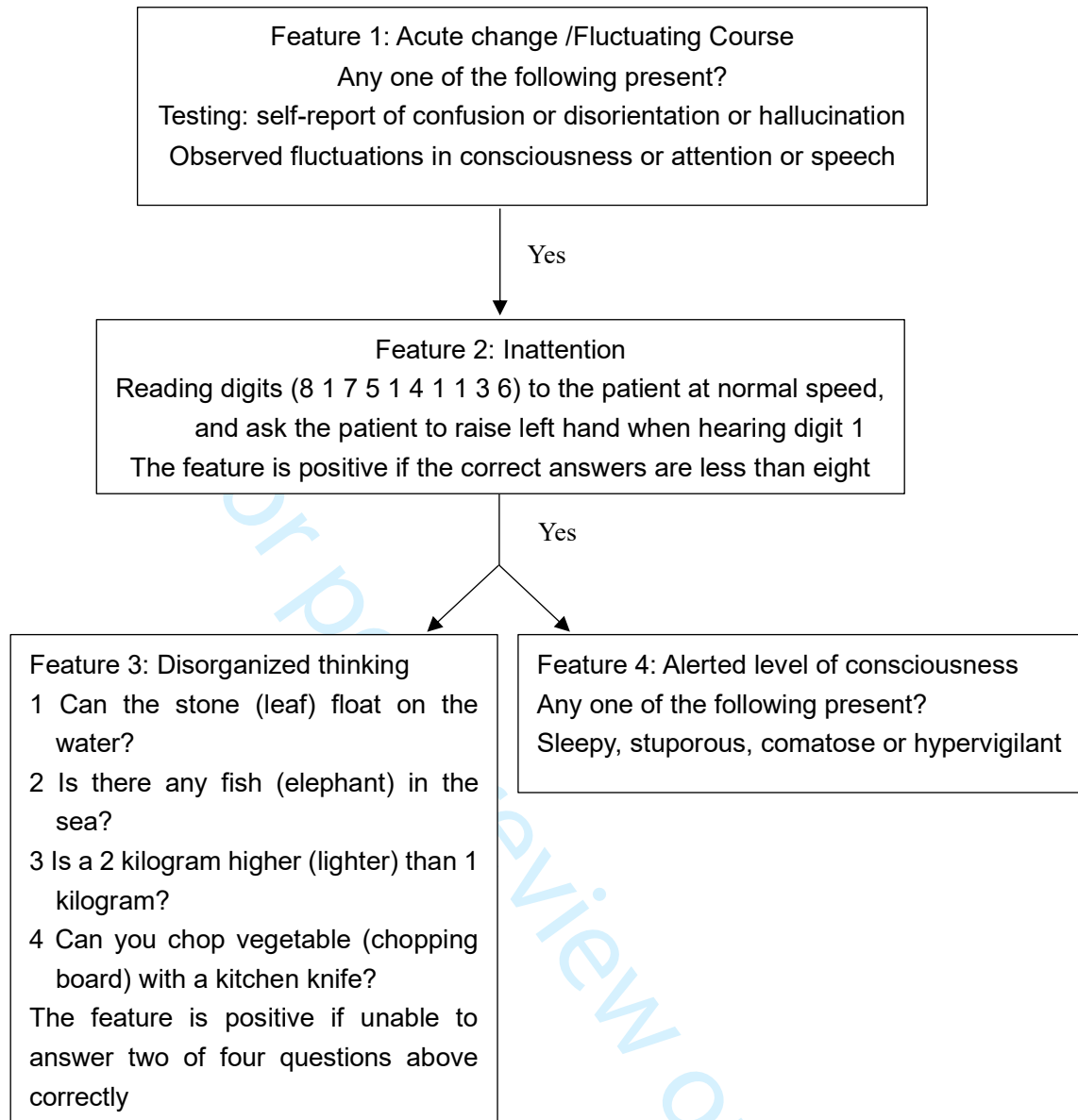
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**Figure 1.** Consolidated Standards of Reporting Trials (CONSORT) flow diagram



**Figure 2.** Overview of 3-minute diagnostic confusion assessment method (3D-CAM) assessment.

Supplementary table 1 Richmond agitation-sedation scale

Score	Term	Description
+4	Combative	Overtly combative or violate; immediate danger to staff
+3	Very agitated	Pulls on 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 (>10 seconds) awakening (eye-opening/eye contact) to voice
-2	Light sedation	Briefly (<10 seconds) awakens with eye contact to voice
-3	Moderate sedation	Movement or eye opening (but no eye contact) to voice
-4	Deep sedation	No response to voice, but any movement to physical stimulation
-5	Unarousable	No response to voice or physical stimulation

Supplementary table 2 CAM-S short form scale\*

Feature	Severity Score		
	Not Present	Present (mild)	Present (marked)
Acute onset & fluctuation course	0	1	—
Inattention	0	1	2
Disorganized thinking	0	1	2
Altered level of consciousness	0	1	2

\*: Rate each symptom of delirium listed in the 3D-CAM as absent (0), mild (1), marked (2). Acute onset & fluctuation course is rated as absent (0) or present (1). Add these scores into a composite. Higher scores indicate more severe delirium.

Supplementary table 3 Chart-based delirium identification instrument

Question	Circle answer
Is there any evidence in the chart of acute confusion (e.g., delirium, mental status change, disorientation, hallucinations, agitation etc.)? Review entire medical record, including progress notes, nursing notes, consult notes, etc.	Yes No Uncertain
What is the source of information about the first episode of acute confusion?	Nurse's notes Physician's notes Other (specify): _____
Approximate time of onset first episode of acute confusion? Check nurse's notes, progress notes, orders, laboratories, for the earliest time referable to the event.	Date: ___ ___ / ___ ___ / ___ ___ Month Day Year Time: ___ : ___ am/pm Uncertain

Supplementary table 4 Telephone interview for cognitive status-40 (TICS-40) instrument  
Chinese version

Item	Score
What is today's date?	5
What is your address?	3
Counting backwards from 20 to 1	2
Repeating following 10 words: ball, flag, woods, watch, television, cellphone, scissor, pillow, pen, whip	10
Subtracting 7 from 100, 93, 86, 79, 72, 65	5
What do people usually use to cut paper?	2
Say this "no pains, no gains"	1
President's and prime minister's name	2
Recalling 10 words above mentioned	10

# Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

## Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. *BMJ*. 2013;346:e7586

		Reporting Item	Page Number
<b>Administrative information</b>			
Title	<a href="#">#1</a>	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	<a href="#">#2a</a>	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	<a href="#">#2b</a>	All items from the World Health Organization Trial Registration Data Set	
Protocol version	<a href="#">#3</a>	Date and version identifier	6
Funding	<a href="#">#4</a>	Sources and types of financial, material, and other support	20
Roles and responsibilities: contributorship	<a href="#">#5a</a>	Names, affiliations, and roles of protocol contributors	1,19



1	Roles and	<a href="#">#5b</a>	Name and contact information for the trial sponsor	1
2	responsibilities:			
3	sponsor contact			
4	information			
5				
6				
7				
8	Roles and	<a href="#">#5c</a>	Role of study sponsor and funders, if any, in study design;	19
9	responsibilities:		collection, management, analysis, and interpretation of data;	
10	sponsor and funder		writing of the report; and the decision to submit the report for	
11			publication, including whether they will have ultimate	
12			authority over any of these activities	
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16	Roles and	<a href="#">#5d</a>	Composition, roles, and responsibilities of the coordinating	
17	responsibilities:		centre, steering committee, endpoint adjudication committee,	
18	committees		data management team, and other individuals or groups	
19			overseeing the trial, if applicable (see Item 21a for data	
20			monitoring committee)	
21				
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23				
24	<b>Introduction</b>			
25				
26				
27	Background and	<a href="#">#6a</a>	Description of research question and justification for	3
28	rationale		undertaking the trial, including summary of relevant studies	
29			(published and unpublished) examining benefits and harms	
30			for each intervention	
31				
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34	Background and	<a href="#">#6b</a>	Explanation for choice of comparators	4,5
35	rationale: choice of			
36	comparators			
37				
38				
39	Objectives	<a href="#">#7</a>	Specific objectives or hypotheses	5,6
40				
41	Trial design	<a href="#">#8</a>	Description of trial design including type of trial (eg, parallel	6
42			group, crossover, factorial, single group), allocation ratio, and	
43			framework (eg, superiority, equivalence, non-inferiority,	
44			exploratory)	
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48	<b>Methods:</b>			6
49	<b>Participants,</b>			
50	<b>interventions, and</b>			
51	<b>outcomes</b>			
52				
53				
54				
55	Study setting	<a href="#">#9</a>	Description of study settings (eg, community clinic, academic	6
56			hospital) and list of countries where data will be collected.	
57			Reference to where list of study sites can be obtained	
58				
59				
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1	Eligibility criteria	<a href="#">#10</a>	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7
2				
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4				
5				
6	Interventions:	<a href="#">#11a</a>	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10
7	description			
8				
9				
10				
11	Interventions:	<a href="#">#11b</a>	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)	10
12	modifications			
13				
14				
15				
16				
17				
18	Interventions:	<a href="#">#11c</a>	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	
19	adherence			
20				
21				
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23				
24	Interventions:	<a href="#">#11d</a>	Relevant concomitant care and interventions that are permitted or prohibited during the trial	8
25	concomitant care			
26				
27				
28	Outcomes	<a href="#">#12</a>	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	12,13
29				
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39	Participant timeline	<a href="#">#13</a>	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	6,7
40				
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46	Sample size	<a href="#">#14</a>	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	16
47				
48				
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51				
52	Recruitment	<a href="#">#15</a>	Strategies for achieving adequate participant enrolment to reach target sample size	6
53				
54				
55				

## Methods:

### Assignment of

**interventions (for  
controlled trials)**

Allocation: sequence generation	<a href="#">#16a</a>	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	7
Allocation concealment mechanism	<a href="#">#16b</a>	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	8
Allocation: implementation	<a href="#">#16c</a>	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8
Blinding (masking)	<a href="#">#17a</a>	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	7,8
Blinding (masking): emergency unblinding	<a href="#">#17b</a>	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	8
<b>Methods: Data collection, management, and analysis</b>			
Data collection plan	<a href="#">#18a</a>	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	11,12
Data collection plan: retention	<a href="#">#18b</a>	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

1	Data management	<a href="#">#19</a>	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	12
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9	Statistics: outcomes	<a href="#">#20a</a>	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	16,17,18
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14	Statistics: additional analyses	<a href="#">#20b</a>	Methods for any additional analyses (eg, subgroup and adjusted analyses)	
15				
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18	Statistics: analysis population and missing data	<a href="#">#20c</a>	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	17
19				
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24	<b>Methods:</b>			
25	<b>Monitoring</b>			
26				
27	Data monitoring: formal committee	<a href="#">#21a</a>	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	20
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37	Data monitoring: interim analysis	<a href="#">#21b</a>	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	
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43	Harms	<a href="#">#22</a>	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	13,14,15
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48	Auditing	<a href="#">#23</a>	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	
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53	<b>Ethics and dissemination</b>			
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57	Research ethics approval	<a href="#">#24</a>	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	2
58				
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1	Protocol amendments	<a href="#">#25</a>	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)	
2				
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8	Consent or assent	<a href="#">#26a</a>	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8
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13	Consent or assent: ancillary studies	<a href="#">#26b</a>	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	
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18	Confidentiality	<a href="#">#27</a>	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	8
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24	Declaration of interests	<a href="#">#28</a>	Financial and other competing interests for principal investigators for the overall trial and each study site	20
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27	Data access	<a href="#">#29</a>	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	12
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33	Ancillary and post trial care	<a href="#">#30</a>	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	
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38	Dissemination policy: trial results	<a href="#">#31a</a>	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	2
39				
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46	Dissemination policy: authorship	<a href="#">#31b</a>	Authorship eligibility guidelines and any intended use of professional writers	2
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50	Dissemination policy: reproducible research	<a href="#">#31c</a>	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	2
51				
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54	<b>Appendices</b>			
55				
56	Informed consent materials	<a href="#">#32</a>	Model consent form and other related documentation given to participants and authorised surrogates	supplemental
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1 Biological specimens [#33](#) Plans for collection, laboratory evaluation, and storage of 14  
2 biological specimens for genetic or molecular analysis in the  
3 current trial and for future use in ancillary studies, if  
4 applicable  
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8 None The SPIRIT Explanation and Elaboration paper is distributed under the terms of the Creative Commons  
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# BMJ Open

**The effects of subanaesthetic S-ketamine on postoperative delirium and cognitive function in elderly patients undergoing non-cardiac thoracic surgery: a protocol for a randomised, double-blinded, placebo- and positive-controlled, non-inferiority trial**

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2022-061535.R1
Article Type:	Protocol
Date Submitted by the Author:	12-May-2022
Complete List of Authors:	WEI, WEI; Guangzhou Medical University Affiliated Cancer Hospital, Anesthesiology Zhang, Anyu ; Guangzhou Medical University Affiliated Cancer Hospital Liu, Lv; Guangzhou Medical University Affiliated Cancer Hospital Zheng, Xi; Guangzhou Medical University Affiliated Cancer Hospital Tang, Chunlin; Guangzhou Medical University Affiliated Cancer Hospital Zhou, Ming ; Guangzhou Medical University Affiliated Cancer Hospital Gu, Yu; Guangzhou Medical University Affiliated Cancer Hospital Yao, Yonghua; Guangzhou Medical University Affiliated Cancer Hospital
<b>Primary Subject Heading</b>:	Anaesthesia
Secondary Subject Heading:	Geriatric medicine, Surgery
Keywords:	Delirium & cognitive disorders < PSYCHIATRY, GERIATRIC MEDICINE, Thoracic surgery < SURGERY

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4 1 **The effects of subanaesthetic S-ketamine on postoperative delirium and cognitive**  
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6 2 **function in elderly patients undergoing non-cardiac thoracic surgery: a protocol for**  
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8 3 **a randomised, double-blinded, placebo- and positive-controlled, non-inferiority trial**

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12 4 **(SKED Trial)**

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55 21 **Wei Wei and Anyu Zhang contributed equally to this study and share first authorship**

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58 22 **Word count: 5468**  
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60



## 1 **Abstract**

2 **Introduction:** Postoperative delirium (POD) is a common and distressing complication  
3 after thoracic surgery. S-ketamine has neuroprotective properties as a dissociative  
4 anaesthetic. Emerging literature has indicated that S-ketamine can reduce cognitive  
5 impairment in patients with depression. However, the role of S-ketamine in preventing  
6 postoperative delirium remains unknown. Therefore, this study aims to evaluate the effect  
7 of intraoperative prophylactic S-ketamine compared to that of dexmedetomidine on the  
8 incidence of postoperative delirium in elderly patients undergoing non-cardiac thoracic  
9 surgery.

10 **Methods and analysis:** This will be a randomised, double-blinded, placebo-controlled,  
11 positive-controlled, non-inferiority trial that enrolled patients aged 60 to 90 years  
12 undergoing thoracic surgery. The patients will be randomly allocated in a ratio of 1:1:1 to  
13 S-ketamine, dexmedetomidine, or normal saline placebo groups using computer-  
14 generated randomisation with a block size of six. The primary outcome will be the incidence  
15 of postoperative delirium within four days after surgery and this will be assessed using a  
16 3-Minute Diagnostic Confusion Assessment Method (3D-CAM) twice a day. The severity  
17 and duration of postoperative delirium, the incidence of emergence delirium, postoperative  
18 pain, quality of sleep, cognitive function, and the plasma concentrations of acetylcholine,  
19 brain-derived neurotrophic factor, tumour necrosis factor- $\alpha$  and incidence of adverse  
20 events will be evaluated as secondary outcomes.

21 **Ethics and dissemination:** Ethical approval has been obtained from the Institutional  
22 Review Board of the Cancer Hospital and the Institute of Guangzhou Medical University  
23 (ZN202119). At the end of the trial, we commit to making a public disclosure available,  
24 regardless the outcomes. The public disclosure will include a publication in an appropriate  
25 journal and an oral presentation at academic meetings.

26 **Trial registration number:** ChiCTR2100052750; **NCT05242692**

27 **Key words:** Postoperative delirium; S-ketamine; Dexmedetomidine

## Strengths and limitations

- ▶ In this randomised controlled trial, we will evaluate, for the first time, the prophylactic effect of S-ketamine on postoperative delirium in elderly patients undergoing non-cardiac thoracic surgery.
- ▶ Methodology strengths of this non-inferiority study involve placebo- and positive-comparators, concealed assignment, blinded assessment and representative sample size.
- ▶ It is a pragmatic trial that will occur in a real-world setting with standardised anaesthetic management. Moreover, the study team is equipped with a rich experience in postoperative neurocognitive function assessment.
- ▶ The current trial is launched at special time when inclusion may be constrained by local SARS-CoV-2 pandemic.
- ▶ This is a single-centre study that exclusively involves thoracic surgery; therefore, the generalisability may not be extrapolated.
- ▶ An anticipated non-inferiority margin ratio of 1.5 in our trial may be too large, and consequently, the sample size may be underestimated.

## Introduction

Postoperative delirium (POD) is a neuropsychiatric disorder in elderly patients, manifested as an acute onset of altered and fluctuating consciousness, inattention, and disorganised thinking. POD occurs in hospital up to 1 week postoperatively or until discharge (whichever occurs first), and typically the highest incidence is observed during the first 72 hours. [1] The incidence of POD varies between 4% to 60%, depending on the age and surgical type, although its incidence is underestimated since the hypoactive subtype is not well appreciated. [2-7] Postoperative delirium is associated with prolonged hospital stay, long-term cognitive and social dysfunction, and even death. [8-10] The 1-year survival probability is reduced by approximately 10% for each additional day of postoperative delirium. [11] The pathophysiological mechanisms of delirium have not been well-elucidated, and neuroinflammation remains a topic of mainstream research interest. Furthermore, its development results from the complicated interaction of multifactorial risks,

1 such as pain, opioids, sleep deprivation, and inflammation, which poses a challenge for  
2 the prevention and treatment of postoperative delirium. [12] Although various techniques,  
3 including multi-component non-pharmacological interventions, are suggested to reduce  
4 the risks, there is limited pharmacological methods to reduce the incidence of delirium. [13]

5 Dexmedetomidine is a highly selective  $\alpha$ -2 adrenergic receptor agonist that is associated  
6 with sedative, sympatholytic, and anti-inflammatory effects, and has the highest-ranking  
7 possibility of preventing postoperative delirium in a recent network meta-analysis. [10]  
8 Furthermore, the plausibility of dexmedetomidine's positive effects on postoperative  
9 delirium is enhanced by evidence of less anticholinergic activity and opioid-sparing  
10 properties. [14] Postoperative prophylactic low-dose dexmedetomidine could remarkably  
11 reduce the incidence of delirium during seven days after non-cardiac surgery; [15]  
12 moreover, perioperative infusion of dexmedetomidine halved the incidence of delirium in  
13 the elderly after major cardiac and non-cardiac surgery without the increase in adverse  
14 effects. [16,17] A randomised controlled trial found that intraoperative dexmedetomidine  
15 did not decrease postoperative delirium or affect cognitive function in the elderly  
16 undergoing major non-cardiac surgery. [18] A meta-analysis including 11 RCTs revealed  
17 that perioperative dexmedetomidine reduced the incidence of POD in elderly patients after  
18 non-cardiac surgery, but this came at the cost of an increased incidence of hypotension  
19 and bradycardia. [19] A meta-analysis of 1301 patients undergoing cardiac surgery  
20 revealed that dexmedetomidine decreased postoperative delirium. [20] Nevertheless, this  
21 meta-analysis should be interpreted with caution, because several of the included studies  
22 did not consider delirium as the primary outcome, the methodology of delirium assessment  
23 varied, and dexmedetomidine administration was also inconsistent, with differing doses  
24 and durations. Furthermore, the finding that dexmedetomidine prevents postoperative  
25 delirium is also controversial. In the DECADE trial, continuous infusions of  
26 dexmedetomidine, started at induction and maintained for 24 hours, failed to reduce  
27 delirium in patients recovering from cardiac surgery. Notably, dexmedetomidine non-  
28 significantly aggravated delirium, probably mediated by hypotension. [21] However, the  
29 plausibility that dexmedetomidine prevents POD should be discussed separately, because  
30 physiopathology and incidence of delirium is quite different between non-cardiac surgery

1 and cardiac surgery (frequent cerebral embolism). The heterogenous ways that  
2 dexmedetomidine is administrated (pre- or post-operative or both, bolus, continuous et al)  
3 also complicated the analysis even more. As with all pharmacological treatment options,  
4 the side effects of dexmedetomidine are bradycardia and hypotension in a dose-dependent  
5 manner, and more strikingly in the elderly; hence, close haemodynamic monitoring is  
6 warranted.

7 Ketamine, a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist, is  
8 pharmacologically rationalised as an effective medication for reducing postoperative  
9 delirium, probably due to its neuroprotective properties. Under surgical conditions, the  
10 enhanced AMPA/NMDA signalling caused by the activation of cytokine receptors, and high  
11 mobility group box 1 facilitate an increased influx of glutamate in hippocampal neurones,  
12 which ultimately promotes glutamate toxicity. [22] Ketamine can mitigate neuronal  
13 apoptosis by inhibiting the activation of NMDA receptors and the transduction of excitatory  
14 signals. [23] The assumption of ketamine's beneficial effects on delirium is also  
15 strengthened by evidence of its opioid-sparing and antidepressant effects. Depression and  
16 delirium, induced by similar pathophysiological mechanisms, are thought to overlap. [24,25]  
17 A small sample size of a randomised controlled trial indicated that a low-dose single bolus  
18 of ketamine at induction significantly attenuated delirium after cardiac surgery. However,  
19 the PODCAST study showed that low-dose ketamine failed to decrease postoperative  
20 delirium, pain, and opioid consumption, and generated a dose-dependent increase in the  
21 occurrence of negative experiences. [26] The PRIDE study offered no possibility for  
22 ketamine to prevent postoperative cognitive decline, including delirium. [27]

23 S-ketamine is the S (+) enantiomer of ketamine, which has a higher affinity with aspartate  
24 receptor and  $\mu$  opioid receptor. The anaesthetic potency of S-ketamine is two-fold higher  
25 than that of racemic ketamine, and it has higher in vivo clearance rate characterized by  
26 lower incidence of adverse reactions. [28] Animal experiments showed that S-ketamine,  
27 rather than racemic ketamine, could alleviate the injury of hippocampal neurones exposed  
28 to glutamate in rodents; a subanaesthetic dose of S-ketamine could remarkably mitigate  
29 neuroinflammation by inhibiting microglia proliferation and TLR4/NF- $\kappa$ B signalling pathway  
30 activation, which consequently improved neurocognitive function. [29,30] Additionally, S-

1 ketamine could promote the plasticity of hippocampal neurones and improve the function  
2 of neurones in the prefrontal and hippocampal neural circuits. [31] A study on healthy  
3 volunteers showed that S-ketamine exhibited pro-neuroplastic effects on hippocampal  
4 structure, which may improve cognitive function after surgery. [32] Moreover, a recent  
5 study on human metabolome revealed that S-ketamine decreases the levels of circulating  
6 branched chain amino acids which inhibit the synthesis and release of serotonin and  
7 noradrenaline in the brain. Thus, S-ketamine could, in theory, increase the effects of  
8 serotonin and noradrenaline in the brain, and contribute to the improvement of depression  
9 and cognitive impairment. [33] Furthermore, We hypothesize that the sympathomimetic  
10 and analgesic properties of S-ketamine might partially explain its non-inferior property for  
11 delirium prevention compared to dexmedetomidine. Though S-ketamine has stronger  
12 potency and lower incidence of adverse reactions, the evidence that it reduces the  
13 incidence of postoperative delirium is fairly insufficient.

14 Since the effects of S-ketamine on postoperative delirium are lack of good quality  
15 evidences, we designed the current prospective, randomised, double-blinded, placebo-  
16 and positive-controlled, non-inferiority trial to investigate the effect of intraoperative  
17 prophylactic S-ketamine on postoperative delirium in elderly patients undergoing thoracic  
18 surgery compared to dexmedetomidine.

## 19 **Methods**

### 20 **Study setting and design**

21 This study will be conducted at the Cancer Hospital and Institute of Guangzhou Medical  
22 University (Guangzhou, Guangdong, China, with principal investigator [PI] Dr Yonghua  
23 Yao). The study activities are expected to commence in March 2022 and be completed in  
24 December 2023. The study design is in accordance with the standard protocol items for  
25 randomised trials guidelines. The overall schedule is illustrated in Table 1, and the  
26 Consolidated Standards of Reporting Trials flow diagram is shown in Figure 1. The current  
27 study protocol is the fifth version.

28  
29 Table 1. Schedule of enrolment, interventions, and assessments for the trial

	Enrolment	Allocation	Post-allocation									Closeout
	Preoperative assessment	Allocation	Before induction	recovery	4-hour after surgery	24-hour after surgery	48-hour after surgery	72-hour after surgery	96-hour after surgery	30-day after surgery	60-day after surgery	
TIME POINT	$-T_1$	$T_0$	$T_1$	$T_2$	$F_1$	$F_2$	$F_3$	$F_4$	$F_5$	$F_6$	$F_7$	
<b>ENROLMENT:</b>												
Eligibility screen	X											
Informed consent	X											
Allocation		X										
<b>INTERVENTIONS:</b>												
S-ketamine			←————→									
Dexmedetomidine			←————→									
Normal Saline			←————→									
<b>ASSESSMENTS:</b>												
Postoperative delirium (3D-CAM)					X	X	X	X	X			
Pain severity (NRS)					X	X	X					
Sleep quality (NRS)						X	X	X	X			
Cognitive function (TICS-40)										X	X	
Haemodynamic variables			←————→									
Emergence delirium (RASS)				X								
Plasma biomarkers (ACh, BDNF, TNF- $\alpha$ )			X	X					X			

1

## 2 Participant recruitment

### 3 Inclusion criteria

- 4 1. Aged 60 to 90 years old.
- 5 2. Both sexes.
- 6 3. American Society of Anaesthesiologists (ASA) physical status classification I-III.
- 7 4. Diagnosed with pulmonary, oesophageal or mediastinal disorders.
- 8 5. Undergoing open or video-assisted thoracic surgery, including lobectomy,
- 9 segmentectomy, pneumonectomy, oesophagectomy, or resection of the mediastinal
- 10 tumour.
- 11 6. General anaesthesia with one lung ventilation (OLV) or bronchial blocker.
- 12 7. An expected operation duration of 2 hours or more.

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4 1 8. Voluntary participation in the trial and signed informed consent.

5  
6 2 **Exclusion criteria**

7 3 1. History of psychiatric disease or severe depression.

8  
9 4 2. History of glaucoma or hyperthyroidism.

10  
11 5 3. History of severe hepatic (Child-Pugh grade C) or renal (requirement for renal  
12 replacement therapy) disorders.

13  
14 6 4. Body mass index (BMI) > 35 kg/m<sup>2</sup>.

15  
16 7 5. Dementia history or baseline Mini-Mental State Examination (MMSE) score of < 23.

17  
18 8 6. Severe audio-visual impairments, or inability to speak Mandarin or Cantonese  
19 precluding communication.

20  
21 9 7. Sinus bradycardia (heart rate < 50 beats per minute, bpm), sick sinus or Wolff-  
22 Parkinson-White syndrome, or 2nd degree atrioventricular block and over.

23  
24 10 8. Uncontrolled hypertension (baseline value > 200/110 mm Hg).

25  
26 11 9. Allergic to dexmedetomidine or S-ketamine.

27  
28 12 10. Taking sedatives, antidepressants or glucocorticoids.

29  
30 13 11. Alcohol or illicit drug misuse disorder.

31  
32 14 12. Life expectancy of less than two months due to extensive tumour metastasis.

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39 15 **Participants consent**

40 16 All patients scheduled for thoracic surgery will be screened one day before the operation  
41 for eligibility at the preoperative evaluation clinic (or on Friday for those who will undergo  
42 surgery the following Monday). Eligible patients will be informed by the study team  
43 coordinator. For the sake of voluntary participation, all patients will be informed about the  
44 aims, procedures, benefits, possible risks of study, and how to react if risks occur. If  
45 interested in enrolment, the patients or their next of kin will sign the written consent form  
46 in triplicate.  
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57 17 **Randomisation and blindness**

58 18 A randomisation code will be generated in a block size of six on the website of  
59 <http://www.Randomization.com> and kept in a sealed opaque envelope by an anaesthetist  
60

1 nurse. The patients will be randomly allocated by a ratio of 1:1:1 to the S-ketamine group  
2 (S group), dexmedetomidine group (D group), or control group (C group) by an anaesthetist  
3 nurse. Dispensing and labelling of the study drugs will be performed by a pharmacist. Both  
4 the anaesthetist nurse and the pharmacist will not be involved in the following research or  
5 follow-up. The randomisation protocol will be kept secure by the anaesthetist nurse. The  
6 primary investigator, and the clinicians collecting the data, are allowed to unmask the  
7 randomization protocol only when both recruitment and the database are closed.

8 The labelled "Study medication" syringes (50 ml), identical in appearance, and the  
9 infusion regimen formulated by the pharmacist based on the randomisation, will be  
10 distributed to the attending anaesthesiologists responsible for anaesthetic management as  
11 soon as the research team informs the central pharmacy about the patient heading for  
12 surgery. In order to avoid anaesthesiologists' speculation about the randomised  
13 assignment, the study drugs will be infused at the same rate (see Table 2). The  
14 anaesthesiologists, patients, investigators responsible for follow-up, and statisticians will  
15 be all blinded to the randomised allocations until the final statistical analyses are completed.  
16 The blindness will be unmasked by the primary investigator in a medical emergency,  
17 including deterioration of the patient's condition intraoperatively or adverse events  
18 postoperatively.

#### 20 **Standard anaesthetic management**

21 On the day of the operation, the patients will be admitted to the operating room after  
22 random assignment. Vital signs will be routinely monitored, including heart rate (HR), blood  
23 pressure (BP), oxyhaemoglobin saturation by pulse oximetry (SpO<sub>2</sub>), end-tidal carbon  
24 dioxide partial pressure (EtCO<sub>2</sub>), nasopharyngeal temperature, and urine output  
25 throughout surgery. Pre-oxygenation with 100% oxygen for 15 min before the induction of  
26 anaesthesia will be delivered to the patient using a face mask. Atropine will be  
27 administered intravenously in avoidance of excessive secretions.

28 After arterial line and central venous line are cannulated under ultrasound guidance,  
29 anaesthesia induction will be performed by administration of midazolam (0.05 mg/kg),  
30 propofol (1-2 mg/kg) or etomidate (0.2 mg/kg), and sufentanil (0.2-0.4 µg/kg). After the



1 patient becomes unconscious, rocuronium (0.6 mg/kg) will be injected intravenously.  
2 Bronchial intubation will be performed smoothly with a video laryngoscope after 3-minute  
3 positive pressure ventilation. The tip of double lumen tubes (DLTs) will be inserted into the  
4 glottis under direct vision and advanced until a mild resistance is perceived. After the  
5 fiberoptic bronchoscope is fully lubricated, it will be advanced into the tracheal lumen of  
6 the DLTs until the carina is identified. Afterwards, the ideal position of the bronchial lumen  
7 (the blue bronchial cuff should be invisible for left DLTs, the opening in the upper lobe of  
8 the right lung should be visible for right DLTs) will be verified. Dual-controlled ventilator  
9 modes (i.e. pressure-controlled ventilation with volume guaranteed or pressure-regulated  
10 volume control) will be applied. One-lung protective ventilation regimen will be conducted  
11 by a combination of tidal volumes ( $V_t$ ) of 6 ml/kg or lower, by predicted body weight, with  
12 a positive end-expiratory pressure of 6 cmH<sub>2</sub>O or beyond based upon guidelines and  
13 expert opinion for optimal practice during OLV. [34] High inspiratory fractions of oxygen  
14 ( $FiO_2 > 70\%$ ) will be administered to maintain  $SpO_2$  higher than 94%. In addition,  
15 continuous positive airway pressure (CPAP) regimen will be considered when necessary.  
16 The respiratory rate will be adjusted to maintain  $EtCO_2$  at 35-45 mmHg. Sedative  
17 maintenance will be performed with a TCI (target-controlled infusion) of propofol according  
18 to the Schnider model at a plasma concentration ( $C_p$ ) of 2-3  $\mu$ g/ml to maintain the  
19 bispectral index value between 40 and 60. Analgesic maintenance will be achieved with a  
20 TCI of remifentanil according to the Minto model at a  $C_p$  of 1-6 ng/ml to fluctuate the HR  
21 and BP within the baseline value  $\pm 20\%$ . An intermittent bolus of rocuronium will be  
22 administered to maintain TOF  $< 1$  intraoperatively. Forced air-warm blankets will be used  
23 to ensure an intraoperative body temperature of 36-37°C. The surgeon will implement an  
24 intercostal nerve block (T3-7) with 20 ml of 0.5% ropivacaine under direct thoracoscopic  
25 view before placing a chest tube. The sign of a successful block is the presence of pleural  
26 displacement. All participants will be given hydromorphone (0.015 mg/kg) when a chest  
27 tube is placed for the sake of prophylaxis of hyperalgesia.

28 A patient-controlled analgesia (PCA) device, with hydromorphone (0.15 mg/kg) and  
29 ondansetron (12 mg) in a total volume of 100 ml, will be connected to the intravenous  
30 cannula at the end of surgery. The device is programmed to administer a background dose

of 2 ml/h, as well as a bolus dose of 0.5 ml with a lockout interval of 15 min for 48 hours. Hydromorphone (0.008 mg/kg) will be administered if the numeric rating scale (NRS) score is > 5 despite the PCA regimen. Residual neuromuscular blockade will be routinely reversed with neostigmine (40  $\mu$ g/kg) and atropine (20  $\mu$ g/kg), and the endotracheal tube will be removed when the patients are able to follow verbal commands.

### Study drugs administration

S-ketamine (50 mg, 2 ml) is diluted to 50 ml (1 mg/ml) with 48 ml normal saline; dexmedetomidine (200  $\mu$ g, 2 ml) is diluted to 100 ml (2  $\mu$ g/ml) with 98 ml normal saline; the control group only receives 50 ml normal saline in light of blindness. All drugs are identical in appearance, packaged in identical 50 ml syringes labelled with "Study medications". The loading dose of study drugs will be infused within 10 minutes before induction, and the maintenance dose will be infused at a constant rate continuously until skin closure. In the preliminary trial, we found that a loading dose of 0.4  $\mu$ g/kg dexmedetomidine lead to obvious bradycardia and transient hypertension events. Therefore, we modified the loading dose of dexmedetomidine to 0.2  $\mu$ g/kg; In addition, in order to ensure blindness, the infusion speed of dexmedetomidine is consistent with that of S-ketamine, which also reduces the side effects of dexmedetomidine. The detailed administrative protocol of study drugs is shown in Table 2.

**Table 2 Study drugs and administrative protocol (take a 60 kg patient as an example)**

Group	Concentration	Loading dose	Maintenance dose
S-ketamine	1 mg/ml	0.25 mg/kg	0.1 mg/kg/h
i.e. The administrative protocol of a 60 kg patient will be a loading dose of 15 ml and a maintenance dose of 6ml/h			
Dexmedetomidine	2 $\mu$ g/ml	0.2 $\mu$ g/kg	0.2 $\mu$ g/kg/h
i.e. The administrative protocol of a 60 kg patient will be a loading dose of 15 ml and a maintenance dose of 6 ml/h			
Control	Normal saline	—	—

---

i.e. The administrative protocol of a 60 kg patient will be a loading dose of 15 ml and a maintenance dose of 6 ml/h

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1

## 2 **Data collection**

3 The following data will be collected through patient interviews and abstractions from the  
4 electronic medical record system:

### 5 **Preoperative data collection**

- 6 1. Patient demographic data including age (years), sex, height (cm), weight (kg), BMI  
7 (kg/m<sup>2</sup>), and education level (years).
- 8 2. ASA classification, Charlson comorbidity index, baseline MMSE, and type of surgery.
- 9 3. Plasma biomarker concentrations including acetylcholine (ACh), brain-derived  
10 neurotrophic factor (BDNF) and tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ) before the  
11 administration of study drugs (T1).

### 12 **Intraoperative data collection**

- 13 1. Haemodynamic parameters including HR (bpm), mean arterial pressure (MAP, mmHg),  
14 SpO<sub>2</sub> and BIS value at 15-minute intervals.
- 15 2. Hypotension and bradycardia episodes (see Table 3).
- 16 3. Hypertension and tachycardia episodes (see Table 3).
- 17 4. Duration of desaturation (SpO<sub>2</sub> < 94%, minutes).
- 18 5. The cumulative dosage of noradrenaline ( $\mu$ g) and atropine (mg).
- 19 6. The consumption of propofol (mg) and opioids (converted to morphine milligram  
20 equivalent by Global RPH, MME).
- 21 7. Surgery, anaesthesia and OLV duration (minutes).
- 22 8. Time to extubation (minutes, duration from discontinuation of propofol to removal of  
23 the tracheal tube).
- 24 9. Emergence agitation (Richmond Agitation-Sedation Scale, RASS score  $\geq$  1).
- 25 10. Plasma biomarker concentrations at the end of operation (T2).

### 26 **Postoperative data collection**

- 27 1. Incident postoperative delirium between 4 h after surgery and the 4th postoperative day, and

1  
2  
3  
4 1 twice daily from postoperative day 1 to postoperative day 4 (8:00-10:00 am) with an  
5  
6 2 interval of at least 6 hours.

7 3 2. Severity and duration of delirium.

8  
9 4 3. Postoperative pain at 4 h, 1 and 2 days after surgery.

10  
11 5 4. Consumption of hydromorphone (mg).

12  
13 6 5. Quality of sleep within 4 days after surgery.

14  
15 7 6. Cognitive function at 30 and 60 days after surgery.

16  
17 8 7. Plasma biomarker concentrations at the 4<sup>th</sup> day after surgery (T3).

18  
19 9 Data Safety and Monitoring Committee (DSMB) is consist of three senior  
20  
21 10 anaesthesiologists and one surgeon who are blinded to the study. The DSMB will provide  
22  
23 11 independent oversight of the SKED trial and will review the study data for the participant  
24  
25 12 safety as well as CRF storage. The data will be entered into the Epidata V4.6 database  
26  
27 13 protected by password only accessible to DSMB. Then, the data will be exported from  
28  
29 14 Epidata database to a statistical package for analysis by biostatisticians independent of  
30  
31 15 the study.  
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33 16

## 34 17 **Outcomes**

### 35 18 **Primary outcomes**

36  
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38 19 The primary outcome will be the incidence of postoperative delirium as defined by any  
39  
40 20 positive assessment between 4 h after surgery and the 4<sup>th</sup> postoperative day.

### 41 21 **Secondary outcomes**

42  
43  
44 22 The main secondary outcome will be the subtype, severity and duration of postoperative  
45  
46 23 delirium.

47  
48  
49 24 Other prespecified secondary outcomes will be the incidence of emergence delirium; pain  
50  
51 25 severity at 4 h, 1 and 2 days after surgery; quality of sleep within 4 days after surgery;  
52  
53 26 cognitive function at 30 and 60 days after surgery; plasma biomarker (ACh, BDNF, TNF-  
54  
55 27  $\alpha$ )  
56  
57 28 concentrations at T1-3; and incidence of adverse events.  
58  
59 29

60

## 1 **Measurement of outcomes**

### 2 **Measurement of delirium**

3 Delirium will be assessed using a validated 3-minute diagnostic confusion assessment  
4 method (3D-CAM Chinese version, with a sensitivity of 84%–99% and specificity of 90%–  
5 97%) [35,36] or Confusion Assessment Method for the Intensive Care Unit (CAM-ICU), for  
6 patients who have a tracheal tube or underwent tracheostomy. [37] 3D-CAM resolves the  
7 four diagnostic features of delirium: (1) acute onset and fluctuating course, (2) inattention,  
8 (3) disorganised thinking, and (4) altered level of consciousness. A patient who displays  
9 both features 1 and 2, with either feature 3 or 4, will be diagnosed with delirium (see Figure  
10 2). [35] Delirium assessments will be performed only when patients can be aroused  
11 sufficiently with an RASS score of -3 to 4 (Supplementary Table 1). Patients with  
12 postoperative delirium will be classified into three subtypes. Hyperactive delirium will be  
13 defined when the RASS score ranges from 1 to 4; hypoactive delirium will be defined when  
14 the RASS score ranges from -1 to -3, and mixed delirium will be defined when the RASS  
15 score ranges from 1 to 4 and -1 to -3 alternatively. The severity of postoperative delirium  
16 will be rated using the CAM-Severity short-form scale (Supplementary Table 2). Mild-to-  
17 moderate delirium will be defined as a CAM-S score of 3 to 5, while severe delirium will be  
18 defined as a CAM-S score of 6 to 7. [38]

19 Four investigators who are not involved in perioperative care will be responsible for  
20 postoperative delirium assessments and will be trained by a psychiatrist with regard to  
21 symptoms, diagnosis, and treatment of delirium. Furthermore, the psychiatrist will explain  
22 the protocols of 3D-CAM and CAM-ICU in detail, and will perform the simulation training of  
23 delirium assessment until a kappa value over 0.8 is achieved between investigators and  
24 psychiatrists. The training process will be repeated every 4-6 months throughout the study.  
25 In addition, the chart-based delirium identification instrument with the information primarily  
26 derived from electronic medical records system and recalling descriptions of caregivers  
27 will be employed to detect any cases of delirium in patients that may occur outside of in-  
28 person delirium assessments (Supplementary Table 3). [39]

### 29 **Pain and sleep quality measurement**

30 Postoperative pain at rest and during a cough will be evaluated using an 11-point NRS (0

1 = [no pain], 0 < NRS < 4 [mild pain], 4 ≤ NRS < 7 [moderate pain], 7 ≤ NRS < 10 [severe pain], NRS = 10 [worst pain imaginable]. Postoperative sleep quality will also be evaluated using the NRS (0 = best-quality sleep, 10 = worst-quality sleep).

#### 4 **Cognitive function measurement**

5 Postoperative cognitive function will be assessed using the Chinese version of the Telephone Interview for Cognitive Status-40 (TICS-40). The TICS-40 scale used in this study consists of nine items with a maximum score of 40 points, including the following variables and corresponding points: address (3 points), current date (5 points), counting backwards (2 points), word-list recalling (10 points), subtractions (5 points), object naming (2 points), repetition (1 point), the president and prime minister's names (2 points), and delayed recall of the word list (10 points). A score below 21 will be defined as mild cognitive impairment (Supplementary Table 4). [40]

#### 13 **Biomarkers concentration measurement**

14 Venous blood (approximately 6 ml) will be sampled and stored on ice in vacutainer tubes containing EDTA. Within 30 min, the samples will be centrifuged at 4°C for 20 min at 2000× g to obtain plasma and then stored at -80°C. We will measure ACh, BDNF, and TNF-α levels by enzyme-linked immunosorbent assay method (in accordance to manufacturer's instructions). (Supplementary text for the rationales of biomarkers selected)

#### 20 **Adverse events**

21 An adverse event (AE) can be any unfavourable and unintended symptom or side effect temporally associated with the use of study medications. The potential AEs that may be considered in this trial are bradycardia, hypotension, tachycardia, hypertension, arrhythmia, nystagmus, hypersalivation, euphoria, emergence agitation, hallucinations, and nightmares. It is possible, but very unlikely, that low-dose S-ketamine (50 mg in total) administered intraoperatively will cause these psychiatric effects. Potential adverse events and medical rescue are shown in Table 3. [41]

28 Serious AEs are rare, life-threatening events that may be associated with the study drugs or perioperative incidents, such as death or serious cardio-cerebral vascular events.

1 **Table 3 The definitions of adverse events and corresponding medication rescue**

Adverse events	Severity	Definition	Treatment	
Hypotension (SBP<90 mm Hg or DBP<50 mm Hg or MAP<80% baseline)	Mild	SBP 80-89 mm Hg	Close monitoring	
	Moderate	SBP 70-79 mm Hg>2 min	Noradrenaline 4 $\mu\text{g}$ \$	
	Severe	SBP 60-69 mm Hg>1 min	Noradrenaline 8 $\mu\text{g}$ #	
	Life-threatening	SBP 60-69 mm Hg and unresponsive to noradrenaline or SBP<60 mm Hg	Intensive intervention and suspend the study	
Hypertension (SBP>140 mm Hg or DBP>90 mm Hg or MAP>120% baseline)	Mild	SBP 141-160 mm Hg or DBP 91-100 mm Hg	Close monitoring	
	Moderate	SBP 160-170 mm Hg or DBP 101-110 mm Hg	Urapidil 12.5 mg	
	Severe	>3 min	Urapidil 25 mg or NG 50 $\mu\text{g}$	
		>2 min	Intensive intervention and suspend the study	
Life-threatening	SBP>180 mm Hg or DBP>120 mm Hg and unresponsive to NG			
	Bradycardia (HR<60 bpm)	Mild	HR 55-60 bpm	Close monitoring
		Moderate	HR 50-54 bpm>3 min	Atropine 0.5 mg
		Severe	HR 40-50 bpm>2 min	Atropine 1.0mg
Life-threatening		HR<40 bpm and unresponsive to atropine	Intensive intervention and suspend the study	
Tachycardia (HR>100 bpm)	Mild	HR 90-100 bpm	Close monitoring	
	Moderate	HR 101-110 bpm>3 min	Esmolol 20 mg	
	Severe	HR 111-130 bpm>2 min	Esmolol 40 mg	
	Life-threatening	HR>130 bpm and unresponsive to Esmolol	Intensive intervention and suspend the study	
Hypoxemia (SpO <sub>2</sub> <94%)	Mild	SpO <sub>2</sub> 90%-94%	Close monitoring	
	Moderate	SpO <sub>2</sub> 80%-90%>3 min	CPAP	
	Severe	SpO <sub>2</sub> 70%-79%>2 min	Two-lung ventilation	
	Life-threatening	SpO <sub>2</sub> <70% and unresponsive to two-lung ventilation	Intensive intervention and suspend the study	
Emergence delirium	Mild	RASS 1-2	Limb restraint	
	Severe	RASS 3-4	Propofol 30 mg	
Hallucination/Nystagmus	NA	3D-CAM	Haloperidol 10 mg	

2 3D-CAM, 3 minutes diagnostic confusion assessment method; CPAP, constant positive

3 airway pressure; HR, heart rate; NA, not applicable; NG, nitro-glycerine; RASS, Richmond

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4 1 Agitation-Sedation Scale.

5 2 \$ followed by continuous infusion with 0.01-0.1  $\mu\text{g}/\text{kg}/\text{min}$  when necessary

6 3 # followed by continuous infusion with 0.1-0.2  $\mu\text{g}/\text{kg}/\text{min}$  when necessary  
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## 11 5 **Sample size calculation**

12 6 The sample size was calculated for the main outcome, the incidence of postoperative  
13 7 delirium, using PASS software version 11.0. Based on previous studies and our recently  
14 8 completed data, we estimated that the incidence of POD in elderly patients undergoing  
15 9 non-cardiac thoracic surgery was 40%. [12,42-46] Assuming that dexmedetomidine is  
16 10 associated with a 40% relative reduction in the incidence of postoperative delirium, the  
17 11 non-inferiority margin rate ratio (RR) of S-ketamine versus dexmedetomidine will be set at  
18 12 1.5. [15,27,47,48] To achieve a two-sided type I error of 5% and 80% power, 729  
19 13 participants (243 patients per arm) will be recruited. To accommodate a 5% dropout rate,  
20 14 the final sample size will be 780 (260 patients per arm).  
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## 31 15 32 16 **Statistical methods**

33 17 Kolmogorov-Smirnov test will be used to evaluate the normal distribution of continuous  
34 18 variables. Normally distributed data will be presented as means  $\pm$  standard deviation (SD),  
35 19 and non-normally distributed data will be presented as medians with interquartile ranges.  
36 20 Categorical data will be summarised as counts (proportions).  
37  
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42 21 The absolute standardised difference (ASD) will be used for the comparison of baseline  
43 22 data among the three groups, that is, the absolute difference in means, mean ranks, or  
44 23 proportions divided by the combined SD. Baseline variables with  $\text{ASD} > 0.013$  (i.e.,  $1.96 \times$   
45 24  $\sqrt{(260 + 260 + 260)/(260 \times 260 \times 260)}$ ) are considered to be imbalanced and will be  
46 25 adjusted for in all analyses when necessary.  
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52 26 For the primary outcome, the incidence of postoperative delirium, the intention-to-treat  
53 27 approach and per-protocol (PP) approach will be performed. Pearson's chi-square test will  
54 28 be applied to compare proportions with the primary outcome among groups. The difference  
55 29 among groups will be expressed as RR and 95% confidence interval (CI), while non-  
56 30 inferiority will be identified if the upper limit of 95% CI of RR is  $< 1.5$ . For the secondary



1 outcomes, only the PP approach will be used. Normally distributed data will be analysed  
2 with one-way analysis of variance (ANOVA); Non-normally distributed data will be  
3 analysed with Kruskal-Wallis test. The median difference will be calculated using the  
4 Hodges-Lehmann estimation on the basis of the Kruskal-Wallis test. Adverse events that  
5 are presented as incidences will be compared by calculating the 95% CI of the incidence  
6 difference: incidence (S group) – incidence (D group), and noninferiority will be achieved  
7 if the upper limit of 95% CI is < 5%. The superiority for outcomes will be assessed when  
8 noninferiority is verified.

9 To account for correlation among repeated measurements, such as numeric rating  
10 scores for pain and sleep quality, plasma biomarker concentrations, and cognitive function,  
11 will be compared using generalised estimating equation analysis among groups. The time  
12 to delirium will be calculated with the Kaplan-Meier estimator, and the differences among  
13 groups will be assessed by the log-rank test. The number needed to treat will be estimated  
14 for the primary outcome.

15 Missing values will be adjusted using random forest imputation in the missForest  
16 package. However, missing values, due to fatigue in the assessment or the patient's  
17 inability to cooperate, will be imputed with positive results or means in the corresponding  
18 treatment group and time point. If the patient did not have a delirium assessment at all (e.g.  
19 dropout or death), no values will be imputed. The last assessment is used to replace the  
20 missing value to estimate the incidence of postoperative delirium in patients who are  
21 discharged or die within 4 days, while the missing value of assessment per day does not  
22 need to be replaced.

23 The *P* values and CIs reported from one-way ANOVA and Kruskal-Wallis test will be  
24 considered to illustrate statistical significance if they are less than 0.017 and 98.3%,  
25 respectively, accounting for three pairwise comparisons. The family-wise significance and  
26 CI levels among the three groups will be set at 0.05% and 95%, respectively. For the pain  
27 intensity score, a 1.1 decrease will be considered the minimal clinically important difference.  
28 [49]

29 Analyses will be conducted using IBM SPSS version 25.0 (SPSS Software, Chicago,  
30 IL, USA), R statistics version 4.1.2 (R Project for Statistical Computing), and GraphPad

1 Prism version 8.0 (GraphPad Software, San Diego, CA, USA).

### 2 3 **Ethics and confidentiality**

4 Ethical approval was obtained from the Institutional Review Board of the Cancer Hospital  
5 and the Institute of Guangzhou Medical University (ZN202119). The study has also been  
6 registered at Chictr.org.cn with the identifier ChiCTR2100052750. The personal  
7 information of the participants will not be disclosed unless authorisation is approved. In  
8 addition, each participant will be provided with a unique identity code, the information of  
9 which will be properly secured. The CRF and Epidata database will be retained for a  
10 minimum of 10 years.

### 11 12 **Patient and Public Involvement**

13 No patients or public representatives were involved in the design of this trial.

### 14 15 **Dissemination**

16 At the end of the trial, we commit to making public disclosure available despite the outcome.  
17 Public disclosure will include publication in an appropriate journal or oral presentation at  
18 an academic meeting. The PI will be considered the first or corresponding author. The  
19 investigators who contribute a minimum of four months to the trial will be co-authors;  
20 otherwise, they will be acknowledged in the publication.

### 21 22 **Discussion**

23 Lung cancer ranks first among all malignancies in China, and anatomic pulmonary  
24 resection is a major component of multimodal therapy according to the lung cancer  
25 guidelines. [12] However, more than 40% of patients undergoing lung cancer surgery are  
26 inflicted by severe depression-related psychological suffering postoperatively. [50]  
27 Depression is an independent predictor of postoperative delirium in patients who undergo  
28 orthopaedic and cancer surgeries. [24] Based on its pharmacological mechanisms and  
29 antidepressant effects, we speculate that S-ketamine would be non-inferior to  
30 dexmedetomidine in reducing postoperative delirium to some extent in the elderly, with

1 fewer episodes of hypotension or less opioid consumption. Hypotension is pertinent to  
2 delirium, and minimisation of intraoperative hypotension episodes is recommended to  
3 reduce postoperative delirium. [51] Additionally, the administration of opioids (long-acting  
4 opioids in particular) is closely related to postoperative delirium in a dose-dependent  
5 manner. Hence, it is critical to abate opioid consumption in order to curtail delirium. [8]

6 Although previous studies have demonstrated that ketamine failed to reduce the  
7 incidence of postoperative delirium in patients undergoing major cardiac or non-cardiac  
8 surgery, we will deploy a different administrative protocol to evaluate the effect of an isomer  
9 of ketamine on postoperative delirium accompanied by dexmedetomidine as a positive  
10 comparator and by an optimal sample size. Dexmedetomidine is a highly recommended  
11 agent in the prevention and treatment of postoperative delirium; however, it is commonly  
12 accompanied by hypotension and bradycardia in the elderly. As the prevention of  
13 postoperative delirium is more practical and effective than the treatment itself, creating a  
14 means of prevention for delirium is extraordinarily indispensable. We believe that the  
15 possible result will be one of the following: (1) S-ketamine will be non-inferior to  
16 dexmedetomidine in the prevention of postoperative delirium; meanwhile, more stable  
17 haemodynamics, lower postoperative pain severity, or other beneficial secondary  
18 outcomes will be observed with S-ketamine intervention. Side effects will be compared  
19 between groups, all of which will be our desirables. This suggests that S-ketamine will be  
20 an optimal choice for limiting delirium emergence in the elderly, and further studies should  
21 be performed to evaluate its effect on long-term cognitive function. (2) S-ketamine will be  
22 non-inferior to dexmedetomidine in postoperative delirium prevention with comparable  
23 secondary outcomes; however, it will be accompanied by frequent side effects. This  
24 indicates that S-ketamine will be clinically valueless for delirium prevention, which is also  
25 possible in view of the results from previous studies on ketamine (PODCAST and PRIDe  
26 study). (3) S-ketamine will be inferior to dexmedetomidine in the prevention of  
27 postoperative delirium, which is probably because dexmedetomidine is recognised as the  
28 most effective medication for delirium, and fewer studies have compared the two drugs.

29 The SKED protocol has many limitations. First, the current trial is launched at special  
30 time when inclusion may be constrained by local SARS-CoV-2 pandemic. As such, the

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4 1 research period may take longer than anticipated. Second, this is a single-centre study  
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6 2 that exclusively involves thoracic surgery; therefore, the generalisability may not be  
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8 3 extrapolated. Third, an anticipated non-inferiority margin ratio of 1.5 in our trial may be  
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10 4 too large, and consequently, the sample size may be underestimated. Fourth, a dropout  
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12 5 rate of 5% seems a bit low as adverse events due to dexmedetomidine may be higher than  
13  
14 6 that, if so, we would enlarge the sample size upon approval from the IRB.

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16 7  
17 8 **Authors' contributions** Wei Wei, Anyu Zhang, Xi Zheng, Ming Zhou, and Yonghua Yao  
18  
19 9 participated in the study design. Wei Wei, Anyu Zhang, and Xi Zheng co-drafted the  
20  
21 10 protocol manuscript. Yu Gu and Yonghua Yao contributed to sample size calculation and  
22  
23 11 statistical consultation. Wei Wei and Xi Zheng developed the case report forms and the  
24  
25 12 Epidata database. Wei Wei, Lv Liu, and Chunlin Tang conducted the preliminary trial.  
26  
27 13 Yonghua Yao served as the primary investigator and provided the funding. All authors  
28  
29 14 completed 3D-CAM and CAM-ICU training courses and obtained good clinical practice  
30  
31 15 certificates.

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34  
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43 21 and Institute of Guangzhou Medical University, Guangzhou, Guangdong, China.

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46 22 **Competing interests statement:** All authors have no conflicts of interest to declare.

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49 23 **Patient consent for publication:** Consent obtained directly from patients.

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52 24 **Provenance and peer review:** Not commissioned; externally peer-reviewed.

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## 20 **Figure legends**

21 **Figure 1.** Consolidated Standards of Reporting Trials (CONSORT) flow diagram.

22 **Figure 2.** Overview of 3-minute Diagnostic Confusion Assessment Method (3D-CAM)  
23 assessment.

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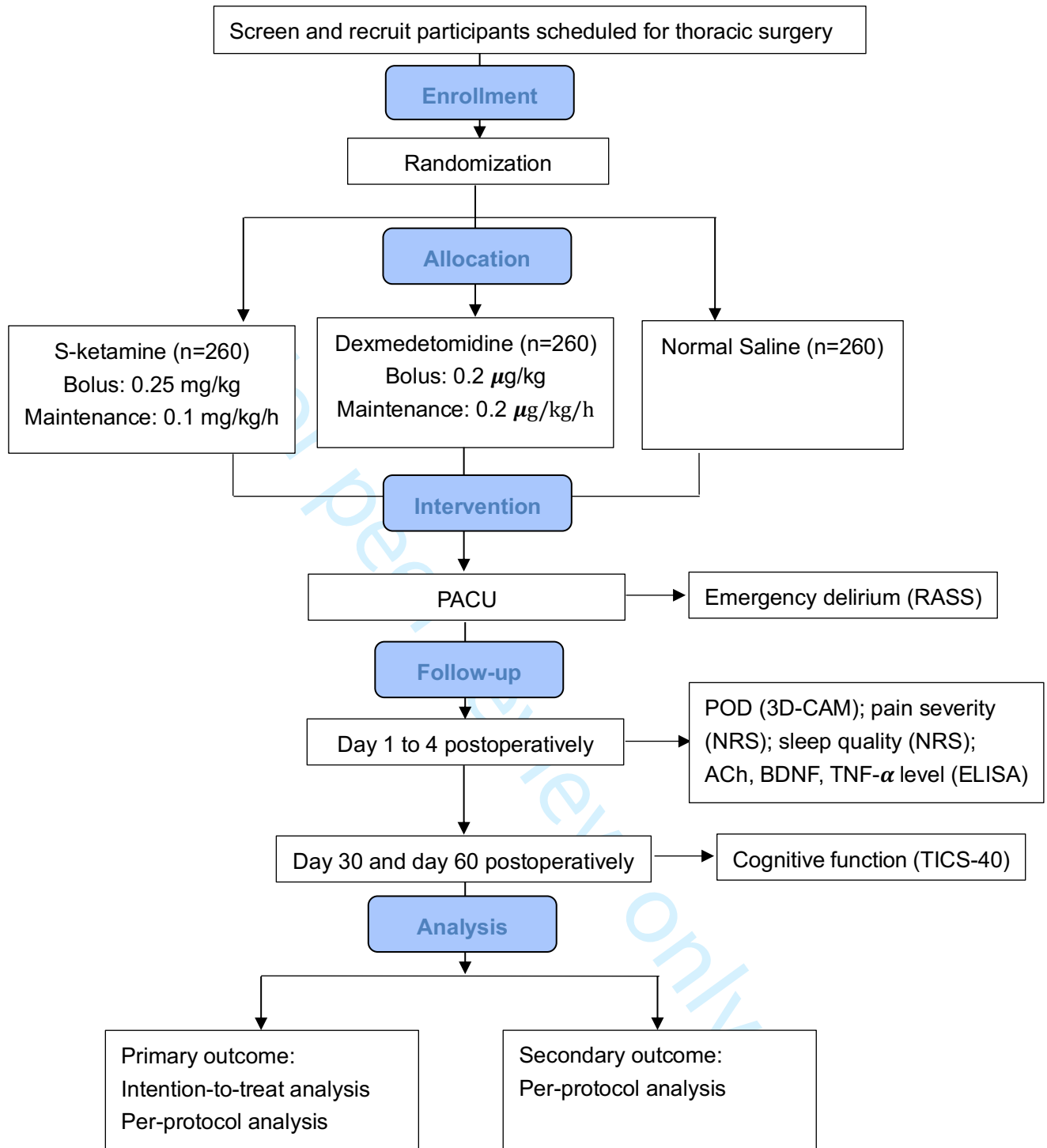
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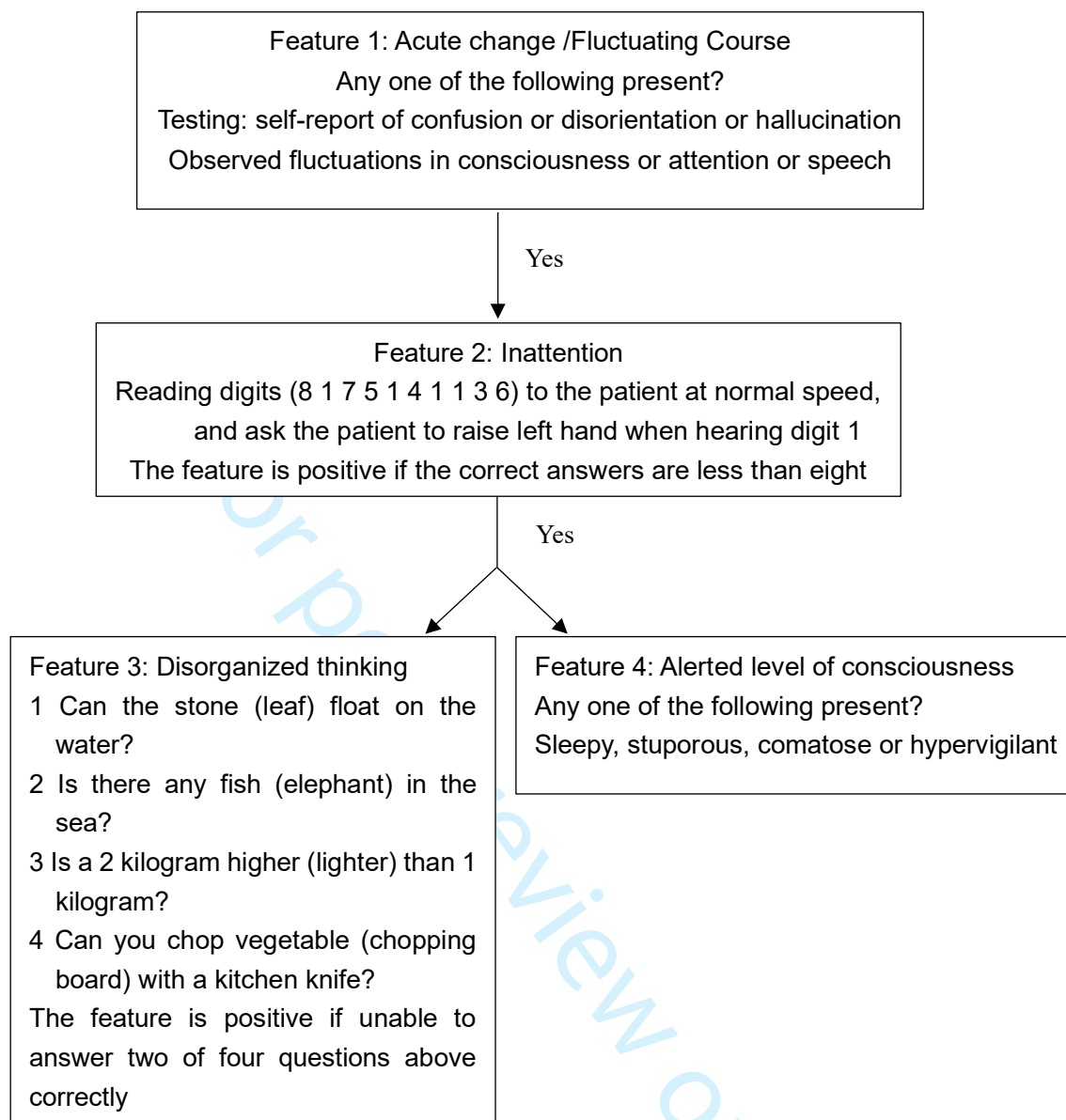
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For peer review only



**Figure 1.** Consolidated Standards of Reporting Trials (CONSORT) flow diagram



**Figure 2.** Overview of 3-minute diagnostic confusion assessment method (3D-CAM) assessment.

Supplementary table 1 Richmond agitation-sedation scale

Score	Term	Description
+4	Combative	Overtly combative or violate; immediate danger to staff
+3	Very agitated	Pulls on 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 (>10 seconds) awakening (eye-opening/eye contact) to voice
-2	Light sedation	Briefly (<10 seconds) awakens with eye contact to voice
-3	Moderate sedation	Movement or eye opening (but no eye contact) to voice
-4	Deep sedation	No response to voice, but any movement to physical stimulation
-5	Unarousable	No response to voice or physical stimulation

Supplementary table 2 CAM-S short form scale\*

Feature	Severity Score		
	Not Present	Present (mild)	Present (marked)
Acute onset & fluctuation course	0	1	—
Inattention	0	1	2
Disorganized thinking	0	1	2
Altered level of consciousness	0	1	2

\*: Rate each symptom of delirium listed in the 3D-CAM as absent (0), mild (1), marked (2). Acute onset & fluctuation course is rated as absent (0) or present (1). Add these scores into a composite. Higher scores indicate more severe delirium.

Supplementary table 3 Chart-based delirium identification instrument

Question	Circle answer
Is there any evidence in the chart of acute confusion (e.g., delirium, mental status change, disorientation, hallucinations, agitation etc.)? Review entire medical record, including progress notes, nursing notes, consult notes, etc.	Yes No Uncertain
What is the source of information about the first episode of acute confusion?	Nurse's notes Physician's notes Other (specify): _____
Approximate time of onset first episode of acute confusion? Check nurse's notes, progress notes, orders, laboratories, for the earliest time referable to the event.	Date: ___ / ___ / ___ Month Day Year Time: ___ : ___ am/pm Uncertain

Supplementary table 4 Telephone interview for cognitive status-40 (TICS-40) instrument  
Chinese version

Item	Score
What is today's date?	5
What is your address?	3
Counting backwards from 20 to 1	2
Repeating following 10 words: ball, flag, woods, watch, television, cellphone, scissor, pillow, pen, whip	10
Subtracting 7 from 100, 93, 86, 79, 72, 65	5
What do people usually use to cut paper?	2
Say this "no pains, no gains"	1
President's and prime minister's name	2
Recalling 10 words above mentioned	10

## Supplementary

The rationales for the biomarkers selected

### 1. The rational for the choice of TNF- $\alpha$

Surgery activates the innate immune system resulting in release of proinflammatory mediators (TNF- $\alpha$ , IL-1 and IL-6). However, ketamine could suppress nuclear factor- $\kappa$ B expression involved in the transcription of genes encoding the proinflammatory cytokines tumour necrosis factor (TNF- $\alpha$ ). [1]

### 2. The rational for the choice of BDNF

BDNF has a role in increasing synaptic plasticity and synaptic function. Reviews have suggested that brain-derived neurotrophic factor (BDNF) improved memory function, reversed age-related changes in brain and prevented cell death. [2] Furthermore, ketamine requires brain-derived neurotrophic factor (BDNF) signals to exert antidepressant effects. [3]

### 3. The rational for the choice of acetylcholine

Acetylcholine is thought to be involved in the neuroplasticity, and is present in several neural pathways responsible for arousal, attention and memory. [4] However, ketamine could increase cholinergic tone that may contribute to the improvement of cognition. [5]

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# Reporting checklist for protocol of a clinical trial.

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## Instructions to authors

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			Page Number
<b>Administrative information</b>			
Title	<a href="#">#1</a>	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	<a href="#">#2a</a>	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	<a href="#">#2b</a>	All items from the World Health Organization Trial Registration Data Set	
Protocol version	<a href="#">#3</a>	Date and version identifier	6
Funding	<a href="#">#4</a>	Sources and types of financial, material, and other support	21
Roles and responsibilities: contributorship	<a href="#">#5a</a>	Names, affiliations, and roles of protocol contributors	1,20



1	Roles and	<a href="#">#5b</a>	Name and contact information for the trial sponsor	1
2	responsibilities:			
3	sponsor contact			
4	information			
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7				
8	Roles and	<a href="#">#5c</a>	Role of study sponsor and funders, if any, in study design;	20
9	responsibilities:		collection, management, analysis, and interpretation of data;	
10	sponsor and funder		writing of the report; and the decision to submit the report for	
11			publication, including whether they will have ultimate	
12			authority over any of these activities	
13				
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16	Roles and	<a href="#">#5d</a>	Composition, roles, and responsibilities of the coordinating	
17	responsibilities:		centre, steering committee, endpoint adjudication committee,	
18	committees		data management team, and other individuals or groups	
19			overseeing the trial, if applicable (see Item 21a for data	
20			monitoring committee)	
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24	<b>Introduction</b>			
25				
26				
27	Background and	<a href="#">#6a</a>	Description of research question and justification for	3
28	rationale		undertaking the trial, including summary of relevant studies	
29			(published and unpublished) examining benefits and harms	
30			for each intervention	
31				
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33				
34	Background and	<a href="#">#6b</a>	Explanation for choice of comparators	4,5
35	rationale: choice of			
36	comparators			
37				
38				
39	Objectives	<a href="#">#7</a>	Specific objectives or hypotheses	5,6
40				
41	Trial design	<a href="#">#8</a>	Description of trial design including type of trial (eg, parallel	6
42			group, crossover, factorial, single group), allocation ratio, and	
43			framework (eg, superiority, equivalence, non-inferiority,	
44			exploratory)	
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47				
48	<b>Methods:</b>			6
49	<b>Participants,</b>			
50	<b>interventions, and</b>			
51	<b>outcomes</b>			
52				
53				
54				
55	Study setting	<a href="#">#9</a>	Description of study settings (eg, community clinic, academic	6
56			hospital) and list of countries where data will be collected.	
57			Reference to where list of study sites can be obtained	
58				
59				
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1	Eligibility criteria	<a href="#">#10</a>	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7-8
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5				
6	Interventions:	<a href="#">#11a</a>	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	11
7	description			
8				
9				
10				
11	Interventions:	<a href="#">#11b</a>	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)	15
12	modifications			
13				
14				
15				
16				
17				
18	Interventions:	<a href="#">#11c</a>	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	
19	adherence			
20				
21				
22				
23				
24	Interventions:	<a href="#">#11d</a>	Relevant concomitant care and interventions that are permitted or prohibited during the trial	8
25	concomitant care			
26				
27				
28	Outcomes	<a href="#">#12</a>	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	12,13
29				
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39	Participant timeline	<a href="#">#13</a>	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	6,7
40				
41				
42				
43				
44				
45				
46	Sample size	<a href="#">#14</a>	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	16
47				
48				
49				
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51				
52	Recruitment	<a href="#">#15</a>	Strategies for achieving adequate participant enrolment to reach target sample size	6
53				
54				
55				

## Methods:

### Assignment of

1 **interventions (for**  
2 **controlled trials)**

3			
4	Allocation: sequence	<a href="#">#16a</a>	Method of generating the allocation sequence (eg, computer-
5	generation		generated random numbers), and list of any factors for
6			stratification. To reduce predictability of a random sequence,
7			details of any planned restriction (eg, blocking) should be
8			provided in a separate document that is unavailable to those
9			who enrol participants or assign interventions
10			
11			
12			
13			
14	Allocation	<a href="#">#16b</a>	Mechanism of implementing the allocation sequence (eg,
15	concealment		central telephone; sequentially numbered, opaque, sealed
16	mechanism		envelopes), describing any steps to conceal the sequence until
17			interventions are assigned
18			
19			
20			
21	Allocation:	<a href="#">#16c</a>	Who will generate the allocation sequence, who will enrol
22	implementation		participants, and who will assign participants to interventions
23			
24	Blinding (masking)	<a href="#">#17a</a>	Who will be blinded after assignment to interventions (eg,
25			trial participants, care providers, outcome assessors, data
26			analysts), and how
27			
28			
29			
30	Blinding (masking):	<a href="#">#17b</a>	If blinded, circumstances under which unblinding is
31	emergency unblinding		permissible, and procedure for revealing a participant's
32			allocated intervention during the trial
33			
34			
35	<b>Methods: Data</b>		
36	<b>collection,</b>		
37	<b>management, and</b>		
38	<b>analysis</b>		
39			
40			
41			
42	Data collection plan	<a href="#">#18a</a>	Plans for assessment and collection of outcome, baseline, and
43			other trial data, including any related processes to promote
44			data quality (eg, duplicate measurements, training of
45			assessors) and a description of study instruments (eg,
46			questionnaires, laboratory tests) along with their reliability
47			and validity, if known. Reference to where data collection
48			forms can be found, if not in the protocol
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50			
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52			
53	Data collection plan:	<a href="#">#18b</a>	Plans to promote participant retention and complete follow-
54	retention		up, including list of any outcome data to be collected for
55			participants who discontinue or deviate from intervention
56			protocols
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1	Data management	<a href="#">#19</a>	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	12-13
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9	Statistics: outcomes	<a href="#">#20a</a>	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	16,17,18
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14	Statistics: additional analyses	<a href="#">#20b</a>	Methods for any additional analyses (eg, subgroup and adjusted analyses)	
15				
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18	Statistics: analysis population and missing data	<a href="#">#20c</a>	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	17
19				
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22				
23				
24	<b>Methods:</b>			
25	<b>Monitoring</b>			
26				
27	Data monitoring: formal committee	<a href="#">#21a</a>	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	20
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37	Data monitoring: interim analysis	<a href="#">#21b</a>	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	
38				
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43	Harms	<a href="#">#22</a>	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	15-16
44				
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48	Auditing	<a href="#">#23</a>	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	
49				
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53	<b>Ethics and dissemination</b>			
54				
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56				
57	Research ethics approval	<a href="#">#24</a>	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	2
58				
59				
60				

1	Protocol amendments	<a href="#">#25</a>	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)	
2				
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8	Consent or assent	<a href="#">#26a</a>	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8
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12				
13	Consent or assent: ancillary studies	<a href="#">#26b</a>	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	
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17				
18	Confidentiality	<a href="#">#27</a>	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	19
19				
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24	Declaration of interests	<a href="#">#28</a>	Financial and other competing interests for principal investigators for the overall trial and each study site	21
25				
26				
27	Data access	<a href="#">#29</a>	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	13
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33	Ancillary and post trial care	<a href="#">#30</a>	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	
34				
35				
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37				
38	Dissemination policy: trial results	<a href="#">#31a</a>	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	2
39				
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46	Dissemination policy: authorship	<a href="#">#31b</a>	Authorship eligibility guidelines and any intended use of professional writers	2
47				
48				
49				
50	Dissemination policy: reproducible research	<a href="#">#31c</a>	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	2
51				
52				
53				
54	<b>Appendices</b>			
55				
56	Informed consent materials	<a href="#">#32</a>	Model consent form and other related documentation given to participants and authorised surrogates	supplemental
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1 Biological specimens [#33](#) Plans for collection, laboratory evaluation, and storage of 15  
2 biological specimens for genetic or molecular analysis in the  
3 current trial and for future use in ancillary studies, if  
4 applicable  
5  
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8 None The SPIRIT Explanation and Elaboration paper is distributed under the terms of the Creative Commons  
9 Attribution License CC-BY-NC. This checklist can be completed online using <https://www.goodreports.org/>, a  
10 tool made by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)  
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# BMJ Open

**The effects of subanaesthetic S-ketamine on postoperative delirium and cognitive function in elderly patients undergoing non-cardiac thoracic surgery: a protocol for a randomised, double-blinded, placebo- and positive-controlled, non-inferiority trial**

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2022-061535.R2
Article Type:	Protocol
Date Submitted by the Author:	06-Jun-2022
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<b>Primary Subject Heading</b>:	Anaesthesia
Secondary Subject Heading:	Geriatric medicine, Surgery
Keywords:	Delirium & cognitive disorders < PSYCHIATRY, GERIATRIC MEDICINE, Thoracic surgery < SURGERY

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Manuscripts

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4 1 **The effects of subanaesthetic S-ketamine on postoperative delirium and cognitive**  
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6 2 **function in elderly patients undergoing non-cardiac thoracic surgery: a protocol for**  
7  
8 3 **a randomised, double-blinded, placebo- and positive-controlled, non-inferiority trial**

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12 4 **(SKED Trial)**

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56 21 **Wei Wei and Anyu Zhang contributed equally to this study and share first authorship**

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58  
59 22 **Word count: 5468**



## 1 **Abstract**

2 **Introduction:** Postoperative delirium (POD) is a common and distressing complication  
3 after thoracic surgery. S-ketamine has neuroprotective properties as a dissociative  
4 anaesthetic. Emerging literature has indicated that S-ketamine can reduce cognitive  
5 impairment in patients with depression. However, the role of S-ketamine in preventing  
6 postoperative delirium remains unknown. Therefore, this study aims to evaluate the effect  
7 of intraoperative prophylactic S-ketamine compared to that of dexmedetomidine on the  
8 incidence of postoperative delirium in elderly patients undergoing non-cardiac thoracic  
9 surgery.

10 **Methods and analysis:** This will be a randomised, double-blinded, placebo-controlled,  
11 positive-controlled, non-inferiority trial that enrolled patients aged 60 to 90 years  
12 undergoing thoracic surgery. The patients will be randomly allocated in a ratio of 1:1:1 to  
13 S-ketamine, dexmedetomidine, or normal saline placebo groups using computer-  
14 generated randomisation with a block size of six. The primary outcome will be the incidence  
15 of postoperative delirium within four days after surgery and this will be assessed using a  
16 3-Minute Diagnostic Confusion Assessment Method (3D-CAM) twice a day. The severity  
17 and duration of postoperative delirium, the incidence of emergence delirium, postoperative  
18 pain, quality of sleep, cognitive function, and the plasma concentrations of acetylcholine,  
19 brain-derived neurotrophic factor, tumour necrosis factor- $\alpha$  and incidence of adverse  
20 events will be evaluated as secondary outcomes.

21 **Ethics and dissemination:** Ethical approval has been obtained from the Institutional  
22 Review Board of the Cancer Hospital and the Institute of Guangzhou Medical University  
23 (ZN202119). At the end of the trial, we commit to making a public disclosure available,  
24 regardless the outcomes. The public disclosure will include a publication in an appropriate  
25 journal and an oral presentation at academic meetings.

26 **Trial registration number:** ChiCTR2100052750; **NCT05242692**

27 **Key words:** Postoperative delirium; S-ketamine; Dexmedetomidine

## Strengths and limitations

- ▶ In this randomised controlled trial, we will evaluate, for the first time, the prophylactic effect of S-ketamine on postoperative delirium in elderly patients undergoing non-cardiac thoracic surgery.
- ▶ Methodology strengths of this non-inferiority study involve placebo- and positive-comparators, concealed assignment, blinded assessment and representative sample size.
- ▶ It is a pragmatic trial that will occur in a real-world setting with standardised anaesthetic management. Moreover, the study team is equipped with a rich experience in postoperative neurocognitive function assessment.
- ▶ This is a single-centre study that exclusively involves thoracic surgery; therefore, the generalisability may not be extrapolated.
- ▶ An anticipated non-inferiority margin ratio of 1.5 in our trial may be too large, and consequently, the sample size may be underestimated.

## Introduction

Postoperative delirium (POD) is a neuropsychiatric disorder in elderly patients, manifested as an acute onset of altered and fluctuating consciousness, inattention, and disorganised thinking. POD occurs in hospital up to 1 week postoperatively or until discharge (whichever occurs first), and typically the highest incidence is observed during the first 72 hours. [1] The incidence of POD varies between 4% to 60%, depending on the age and surgical type, although its incidence is underestimated since the hypoactive subtype is not well appreciated. [2-7] Postoperative delirium is associated with prolonged hospital stay, long-term cognitive and social dysfunction, and even death. [8-10] The 1-year survival probability is reduced by approximately 10% for each additional day of postoperative delirium. [11] The pathophysiological mechanisms of delirium have not been well-elucidated, and neuroinflammation remains a topic of mainstream research interest. Furthermore, its development results from the complicated interaction of multifactorial risks, such as pain, opioids, sleep deprivation, and inflammation, which poses a challenge for the prevention and treatment of postoperative delirium. [12] Although various techniques,

1 including multi-component non-pharmacological interventions, are suggested to reduce  
2 the risks, there is limited pharmacological methods to reduce the incidence of delirium. [13]

3 Dexmedetomidine is a highly selective  $\alpha$ -2 adrenergic receptor agonist that is associated  
4 with sedative, sympatholytic, and anti-inflammatory effects, and has the highest-ranking  
5 possibility of preventing postoperative delirium in a recent network meta-analysis. [10]

6 Furthermore, the plausibility of dexmedetomidine's positive effects on postoperative  
7 delirium is enhanced by evidence of less anticholinergic activity and opioid-sparing  
8 properties. [14] Postoperative prophylactic low-dose dexmedetomidine could remarkably  
9 reduce the incidence of delirium during seven days after non-cardiac surgery; [15]  
10 moreover, perioperative infusion of dexmedetomidine halved the incidence of delirium in  
11 the elderly after major cardiac and non-cardiac surgery without the increase in adverse  
12 effects. [16,17] A randomised controlled trial found that intraoperative dexmedetomidine  
13 did not decrease postoperative delirium or affect cognitive function in the elderly  
14 undergoing major non-cardiac surgery. [18] A meta-analysis including 11 RCTs revealed  
15 that perioperative dexmedetomidine reduced the incidence of POD in elderly patients after  
16 non-cardiac surgery, but this came at the cost of an increased incidence of hypotension  
17 and bradycardia. [19] A meta-analysis of 1301 patients undergoing cardiac surgery  
18 revealed that dexmedetomidine decreased postoperative delirium. [20] Nevertheless, this  
19 meta-analysis should be interpreted with caution, because several of the included studies  
20 did not consider delirium as the primary outcome, the methodology of delirium assessment  
21 varied, and dexmedetomidine administration was also inconsistent, with differing doses  
22 and durations. Furthermore, the finding that dexmedetomidine prevents postoperative  
23 delirium is also controversial. In the DECADE trial, continuous infusions of  
24 dexmedetomidine, started at induction and maintained for 24 hours, failed to reduce  
25 delirium in patients recovering from cardiac surgery. Notably, dexmedetomidine non-  
26 significantly aggravated delirium, probably mediated by hypotension. [21] However, the  
27 plausibility that dexmedetomidine prevents POD should be discussed separately, because  
28 pathophysiology and incidence of delirium is quite different between non-cardiac surgery  
29 and cardiac surgery (frequent cerebral embolism). The heterogenous ways that  
30 dexmedetomidine is administrated (pre- or post-operative or both, bolus, continuous et al)

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4 1 also complicated the analysis even more. As with all pharmacological treatment options,  
5  
6 2 the side effects of dexmedetomidine are bradycardia and hypotension in a dose-dependent  
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8 3 manner, and more strikingly in the elderly; hence, close haemodynamic monitoring is  
9  
10 4 warranted.

11  
12 5 Ketamine, a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist, is  
13  
14 6 pharmacologically rationalised as an effective medication for reducing postoperative  
15  
16 7 delirium, probably due to its neuroprotective properties. Under surgical conditions, the  
17  
18 8 enhanced AMPA/NMDA signalling caused by the activation of cytokine receptors, and high  
19  
20 9 mobility group box 1 facilitate an increased influx of glutamate in hippocampal neurones,  
21  
22 10 which ultimately promotes glutamate toxicity. [22] Ketamine can mitigate neuronal  
23  
24 11 apoptosis by inhibiting the activation of NMDA receptors and the transduction of excitatory  
25  
26 12 signals. [23] The assumption of ketamine's beneficial effects on delirium is also  
27  
28 13 strengthened by evidence of its opioid-sparing and antidepressant effects. Depression and  
29  
30 14 delirium, induced by similar pathophysiological mechanisms, are thought to overlap. [24,25]  
31  
32 15 A small sample size of a randomised controlled trial indicated that a low-dose single bolus  
33  
34 16 of ketamine at induction significantly attenuated delirium after cardiac surgery. However,  
35  
36 17 the PODCAST study showed that low-dose ketamine failed to decrease postoperative  
37  
38 18 delirium, pain, and opioid consumption, and generated a dose-dependent increase in the  
39  
40 19 occurrence of negative experiences. [26] The PRIDE study offered no possibility for  
41  
42 20 ketamine to prevent postoperative cognitive decline, including delirium. [27] Ketamine  
43  
44 21 remains an off-label treatment for treatment-POD with factors that limit widespread use  
45  
46 22 including its dissociative effects and abuse potential.

47  
48 23 S-ketamine is the S (+) enantiomer of ketamine, which has a higher affinity with aspartate  
49  
50 24 receptor and  $\mu$  opioid receptor. The anaesthetic potency of S-ketamine is two-fold higher  
51  
52 25 than that of racemic ketamine, and it has higher in vivo clearance rate characterized by  
53  
54 26 lower incidence of adverse reactions. [28] Animal experiments showed that S-ketamine,  
55  
56 27 rather than racemic ketamine, could alleviate the injury of hippocampal neurones exposed  
57  
58 28 to glutamate in rodents; a subanaesthetic dose of S-ketamine could remarkably mitigate  
59  
60 29 neuroinflammation by inhibiting microglia proliferation and TLR4/NF- $\kappa$ B signalling pathway  
30 30 activation, which consequently improved neurocognitive function. [29,30] Additionally, S-

1 ketamine could promote the plasticity of hippocampal neurones and improve the function  
2 of neurones in the prefrontal and hippocampal neural circuits. [31] A study on healthy  
3 volunteers showed that S-ketamine exhibited pro-neuroplastic effects on hippocampal  
4 structure, which may improve cognitive function after surgery. [32] Moreover, a recent  
5 study on human metabolome revealed that S-ketamine decreases the levels of circulating  
6 branched chain amino acids which inhibit the synthesis and release of serotonin and  
7 noradrenaline in the brain. Thus, S-ketamine could, in theory, increase the effects of  
8 serotonin and noradrenaline in the brain, and contribute to the improvement of depression  
9 and cognitive impairment. [33] Furthermore, we hypothesize that the sympathomimetic  
10 and analgesic properties of S-ketamine might partially explain its non-inferior property for  
11 delirium prevention compared to dexmedetomidine. Though S-ketamine has stronger  
12 potency and lower incidence of adverse reactions, the evidence that it reduces the  
13 incidence of postoperative delirium is fairly insufficient.

14 Since the effects of S-ketamine on postoperative delirium are lack of good quality  
15 evidences, we designed the current prospective, randomised, double-blinded, placebo-  
16 and positive-controlled, non-inferiority trial to investigate the effect of intraoperative  
17 prophylactic S-ketamine on postoperative delirium in elderly patients undergoing thoracic  
18 surgery compared to dexmedetomidine.

## 19 **Methods**

### 20 **Study setting and design**

21 This study will be conducted at the Cancer Hospital and Institute of Guangzhou Medical  
22 University (Guangzhou, Guangdong, China, with principal investigator [PI] Dr Yonghua  
23 Yao). The study activities are expected to commence in March 2022 and be completed in  
24 December 2023. The study design is in accordance with the standard protocol items for  
25 randomised trials guidelines. The overall schedule is illustrated in Table 1, and the  
26 Consolidated Standards of Reporting Trials flow diagram is shown in Figure 1. The current  
27 study protocol is the fifth version.

28  
29 Table 1. Schedule of enrolment, interventions, and assessments for the trial

	Enrolment	Allocation	Post-allocation									Closeout
	Preoperative assessment	Allocation	Before induction	recovery	4-hour after surgery	24-hour after surgery	48-hour after surgery	72-hour after surgery	96-hour after surgery	30-day after surgery	60-day after surgery	
TIME POINT	$-T_1$	$T_0$	$T_1$	$T_2$	$F_1$	$F_2$	$F_3$	$F_4$	$F_5$	$F_6$	$F_7$	
<b>ENROLMENT:</b>												
Eligibility screen	X											
Informed consent	X											
Allocation		X										
<b>INTERVENTIONS:</b>												
S-ketamine			←————→									
Dexmedetomidine			←————→									
Normal Saline			←————→									
<b>ASSESSMENTS:</b>												
Postoperative delirium (3D-CAM)					X	X	X	X	X			
Pain severity (NRS)					X	X	X					
Sleep quality (NRS)						X	X	X	X			
Cognitive function (TICS-40)										X	X	
Haemodynamic variables			←————→									
Emergence delirium (RASS)				X								
Plasma biomarkers (ACh, BDNF, TNF- $\alpha$ )			X	X					X			

1

## 2 Participant recruitment

### 3 Inclusion criteria

- 4 1. Aged 60 to 90 years old.
- 5 2. Both sexes.
- 6 3. American Society of Anaesthesiologists (ASA) physical status classification I-III.
- 7 4. Diagnosed with pulmonary, oesophageal or mediastinal disorders.
- 8 5. Undergoing open or video-assisted thoracic surgery, including lobectomy,
- 9 segmentectomy, pneumonectomy, oesophagectomy, or resection of the mediastinal
- 10 tumour.
- 11 6. General anaesthesia with one lung ventilation (OLV) or bronchial blocker.
- 12 7. An expected operation duration of 2 hours or more.

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4 1 8. Voluntary participation in the trial and signed informed consent.

5  
6 2 **Exclusion criteria**

7 3 1. History of severe psychiatric disease.

8  
9 4 2. History of glaucoma or hyperthyroidism.

10  
11 5 3. History of severe hepatic (Child-Pugh grade C) or renal (requirement for renal  
12 replacement therapy) disorders.

13  
14 6 4. Body mass index (BMI) > 35 kg/m<sup>2</sup>.

15  
16 7 5. Dementia history or baseline Mini-Mental State Examination (MMSE) score of < 23.

17  
18 8 6. Severe audio-visual impairments, or inability to speak Mandarin or Cantonese  
19 precluding communication.

20  
21 9 7. Sinus bradycardia (heart rate < 50 beats per minute, bpm), sick sinus or Wolff-  
22 Parkinson-White syndrome, or 2nd degree atrioventricular block and over.

23  
24 10 8. Uncontrolled hypertension (baseline value > 200/110 mm Hg).

25  
26 11 9. Allergic to dexmedetomidine or S-ketamine.

27  
28 12 10. Taking sedatives, antidepressants or glucocorticoids.

29  
30 13 11. Alcohol or illicit drug misuse disorder.

31  
32 14 12. Life expectancy of less than two months due to extensive tumour metastasis.

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39 19 **Participants consent**

40 20 All patients scheduled for thoracic surgery will be screened one day before the operation  
41 for eligibility at the preoperative evaluation clinic (or on Friday for those who will undergo  
42 surgery the following Monday). Eligible patients will be informed by the study team  
43 coordinator. For the sake of voluntary participation, all patients will be informed about the  
44 aims, procedures, benefits, possible risks of study, and how to react if risks occur. If  
45 interested in enrolment, the patients or their next of kin will sign the written consent form  
46 in triplicate.  
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57 28 **Randomisation and blindness**

58 29 A randomisation code will be generated in a block size of six on the website of  
59 <http://www.Randomization.com> and kept in a sealed opaque envelope by an anaesthetist  
60

1 nurse. The patients will be randomly allocated by a ratio of 1:1:1 to the S-ketamine group  
2 (S group), dexmedetomidine group (D group), or control group (C group) by an anaesthetist  
3 nurse. Dispensing and labelling of the study drugs will be performed by a pharmacist. Both  
4 the anaesthetist nurse and the pharmacist will not be involved in the following research or  
5 follow-up. The randomisation protocol will be kept secure by the anaesthetist nurse. The  
6 primary investigator, and the clinicians collecting the data, are allowed to unmask the  
7 randomization protocol only when both recruitment and the database are closed.

8 The labelled "Study medication" syringes (50 ml), identical in appearance, and the  
9 infusion regimen formulated by the pharmacist based on the randomisation, will be  
10 distributed to the attending anaesthesiologists responsible for anaesthetic management as  
11 soon as the research team informs the central pharmacy about the patient heading for  
12 surgery. In order to avoid anaesthesiologists' speculation about the randomised  
13 assignment, the study drugs will be infused at the same rate (see Table 2). The  
14 anaesthesiologists, patients, investigators responsible for follow-up, and statisticians will  
15 be all blinded to the randomised allocations until the final statistical analyses are completed.  
16 The blindness will be unmasked by the primary investigator in a medical emergency,  
17 including deterioration of the patient's condition intraoperatively or adverse events  
18 postoperatively.

#### 20 **Standard anaesthetic management**

21 On the day of the operation, the patients will be admitted to the operating room after  
22 random assignment. Vital signs will be routinely monitored, including heart rate (HR), blood  
23 pressure (BP), oxyhaemoglobin saturation by pulse oximetry (SpO<sub>2</sub>), end-tidal carbon  
24 dioxide partial pressure (EtCO<sub>2</sub>), nasopharyngeal temperature, and urine output  
25 throughout surgery. Pre-oxygenation with 100% oxygen for 15 min before the induction of  
26 anaesthesia will be delivered to the patient using a face mask. Atropine will be  
27 administered intravenously in avoidance of excessive secretions.

28 After arterial line and central venous line are cannulated under ultrasound guidance,  
29 anaesthesia induction will be performed by administration of midazolam (0.05 mg/kg),  
30 propofol (1-2 mg/kg) or etomidate (0.2 mg/kg), and sufentanil (0.2-0.4 µg/kg). After the



1 patient becomes unconscious, rocuronium (0.6 mg/kg) will be injected intravenously.  
2 Bronchial intubation will be performed smoothly with a video laryngoscope after 3-minute  
3 positive pressure ventilation. The tip of double lumen tubes (DLTs) will be inserted into the  
4 glottis under direct vision and advanced until a mild resistance is perceived. After the  
5 fiberoptic bronchoscope is fully lubricated, it will be advanced into the tracheal lumen of  
6 the DLTs until the carina is identified. Afterwards, the ideal position of the bronchial lumen  
7 (the blue bronchial cuff should be invisible for left DLTs, the opening in the upper lobe of  
8 the right lung should be visible for right DLTs) will be verified. Dual-controlled ventilator  
9 modes (i.e. pressure-controlled ventilation with volume guaranteed or pressure-regulated  
10 volume control) will be applied. One-lung protective ventilation regimen will be conducted  
11 by a combination of tidal volumes ( $V_t$ ) of 6 ml/kg or lower, by predicted body weight, with  
12 a positive end-expiratory pressure of 6 cmH<sub>2</sub>O or beyond based upon guidelines and  
13 expert opinion for optimal practice during OLV. [34] High inspiratory fractions of oxygen  
14 ( $FiO_2 > 70\%$ ) will be administered to maintain  $SpO_2$  higher than 94%. In addition,  
15 continuous positive airway pressure (CPAP) regimen will be considered when necessary.  
16 The respiratory rate will be adjusted to maintain  $EtCO_2$  at 35-45 mmHg. Sedative  
17 maintenance will be performed with a TCI (target-controlled infusion) of propofol according  
18 to the Schnider model at a plasma concentration ( $C_p$ ) of 2-3  $\mu$ g/ml to maintain the  
19 bispectral index value between 40 and 60. Analgesic maintenance will be achieved with a  
20 TCI of remifentanyl according to the Minto model at a  $C_p$  of 1-6 ng/ml to fluctuate the HR  
21 and BP within the baseline value  $\pm 20\%$ . An intermittent bolus of rocuronium will be  
22 administered to maintain TOF  $< 1$  intraoperatively. Forced air-warm blankets will be used  
23 to ensure an intraoperative body temperature of 36-37°C. The surgeon will implement an  
24 intercostal nerve block (T3-7) with 20 ml of 0.5% ropivacaine under direct thoracoscopic  
25 view before placing a chest tube. The sign of a successful block is the presence of pleural  
26 displacement. All participants will be given hydromorphone (0.015 mg/kg) when a chest  
27 tube is placed for the sake of prophylaxis of hyperalgesia.

28 A patient-controlled analgesia (PCA) device, with hydromorphone (0.15 mg/kg) and  
29 ondansetron (12 mg) in a total volume of 100 ml, will be connected to the intravenous  
30 cannula at the end of surgery. The device is programmed to administer a background dose

of 2 ml/h, as well as a bolus dose of 0.5 ml with a lockout interval of 15 min for 48 hours. Hydromorphone (0.008 mg/kg) will be administered if the numeric rating scale (NRS) score is > 5 despite the PCA regimen. Residual neuromuscular blockade will be routinely reversed with neostigmine (40  $\mu$ g/kg) and atropine (20  $\mu$ g/kg), and the endotracheal tube will be removed when the patients are able to follow verbal commands.

### Study drugs administration

S-ketamine (50 mg, 2 ml) is diluted to 50 ml (1 mg/ml) with 48 ml normal saline; dexmedetomidine (200  $\mu$ g, 2 ml) is diluted to 100 ml (2  $\mu$ g/ml) with 98 ml normal saline; the control group only receives 50 ml normal saline in light of blindness. All drugs are identical in appearance, packaged in identical 50 ml syringes labelled with "Study medications". The loading dose of study drugs will be infused within 10 minutes before induction, and the maintenance dose will be infused at a constant rate continuously until skin closure. In the preliminary trial, we found that a loading dose of 0.4  $\mu$ g/kg dexmedetomidine lead to obvious bradycardia and transient hypertension events. Therefore, we modified the loading dose of dexmedetomidine to 0.2  $\mu$ g/kg; In addition, in order to ensure blindness, the infusion speed of dexmedetomidine is consistent with that of S-ketamine, which also reduces the side effects of dexmedetomidine. The detailed administrative protocol of study drugs is shown in Table 2.

**Table 2 Study drugs and administrative protocol (take a 60 kg patient as an example)**

Group	Concentration	Loading dose	Maintenance dose
S-ketamine	1 mg/ml	0.25 mg/kg	0.1 mg/kg/h
i.e. The administrative protocol of a 60 kg patient will be a loading dose of 15 ml and a maintenance dose of 6ml/h			
Dexmedetomidine	2 $\mu$ g/ml	0.2 $\mu$ g/kg	0.2 $\mu$ g/kg/h
i.e. The administrative protocol of a 60 kg patient will be a loading dose of 15 ml and a maintenance dose of 6 ml/h			
Control	Normal saline	—	—

---

i.e. The administrative protocol of a 60 kg patient will be a loading dose of 15 ml and a maintenance dose of 6 ml/h

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1

## 2 **Data collection**

3 The following data will be collected through patient interviews and abstractions from the  
4 electronic medical record system:

### 5 **Preoperative data collection**

- 6 1. Patient demographic data including age (years), sex, height (cm), weight (kg), BMI  
7 (kg/m<sup>2</sup>), and education level (years).
- 8 2. ASA classification, Charlson comorbidity index, baseline MMSE, and type of surgery.
- 9 3. Plasma biomarker concentrations including acetylcholine (ACh), brain-derived  
10 neurotrophic factor (BDNF) and tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ) before the  
11 administration of study drugs (T1).

### 12 **Intraoperative data collection**

- 13 1. Haemodynamic parameters including HR (bpm), mean arterial pressure (MAP, mmHg),  
14 SpO<sub>2</sub> and BIS value at 15-minute intervals.
- 15 2. Hypotension and bradycardia episodes (see Table 3).
- 16 3. Hypertension and tachycardia episodes (see Table 3).
- 17 4. Duration of desaturation (SpO<sub>2</sub> < 94%, minutes).
- 18 5. The cumulative dosage of noradrenaline ( $\mu$ g) and atropine (mg).
- 19 6. The consumption of propofol (mg) and opioids (converted to morphine milligram  
20 equivalent by Global RPH, MME).
- 21 7. Surgery, anaesthesia and OLV duration (minutes).
- 22 8. Time to extubation (minutes, duration from discontinuation of propofol to removal of  
23 the tracheal tube).
- 24 9. Emergence agitation (Richmond Agitation-Sedation Scale, RASS score  $\geq$  1).
- 25 10. Plasma biomarker concentrations at the end of operation (T2).

### 26 **Postoperative data collection**

- 27 1. Incident postoperative delirium between 4 h after surgery and the 4th postoperative day, and

1  
2  
3  
4 1 twice daily from postoperative day 1 to postoperative day 4 (8:00-10:00 am) with an  
5  
6 2 interval of at least 6 hours.

7 3 2. Severity and duration of delirium.

8  
9 4 3. Postoperative pain at 4 h, 1 and 2 days after surgery.

10  
11 5 4. Consumption of hydromorphone (mg).

12  
13 6 5. Quality of sleep within 4 days after surgery.

14  
15 7 6. Cognitive function at 30 and 60 days after surgery.

16  
17 8 7. Plasma biomarker concentrations at the 4<sup>th</sup> day after surgery (T3).

18  
19 9 Data Safety and Monitoring Committee (DSMB) is consist of three senior  
20  
21 10 anaesthesiologists and one surgeon who are blinded to the study. The DSMB will provide  
22  
23 11 independent oversight of the SKED trial and will review the study data for the participant  
24  
25 12 safety as well as CRF storage. The data will be entered into the Epidata V4.6 database  
26  
27 13 protected by password only accessible to DSMB. Then, the data will be exported from  
28  
29 14 Epidata database to a statistical package for analysis by biostatisticians independent of  
30  
31 15 the study.

32  
33 16

## 34 35 17 **Outcomes**

### 36 37 18 **Primary outcomes**

38  
39 19 The primary outcome will be the incidence of postoperative delirium as defined by any  
40  
41 20 positive assessment between 4 h after surgery and the 4<sup>th</sup> postoperative day.

### 42 43 21 **Secondary outcomes**

44  
45 22 The main secondary outcome will be the subtype, severity and duration of postoperative  
46  
47 23 delirium.

48  
49 24 Other prespecified secondary outcomes will be the incidence of emergence delirium; pain  
50  
51 25 severity at 4 h, 1 and 2 days after surgery; quality of sleep within 4 days after surgery;  
52  
53 26 cognitive function at 30 and 60 days after surgery; plasma biomarker (ACh, BDNF, TNF-  
54  
55 27  $\alpha$ )  
56  
57 28 concentrations at T1-3; and incidence of adverse events.

58  
59 29  
60

## 1 **Measurement of outcomes**

### 2 **Measurement of delirium**

3 Delirium will be assessed using a validated 3-minute diagnostic confusion assessment  
4 method (3D-CAM Chinese version, with a sensitivity of 84%–99% and specificity of 90%–  
5 97%) [35,36] or Confusion Assessment Method for the Intensive Care Unit (CAM-ICU), for  
6 patients who have a tracheal tube or underwent tracheostomy. [37] 3D-CAM resolves the  
7 four diagnostic features of delirium: (1) acute onset and fluctuating course, (2) inattention,  
8 (3) disorganised thinking, and (4) altered level of consciousness. A patient who displays  
9 both features 1 and 2, with either feature 3 or 4, will be diagnosed with delirium (see Figure  
10 2). [35] Delirium assessments will be performed only when patients can be aroused  
11 sufficiently with an RASS score of -3 to 4 (Supplementary Table 1). Patients with  
12 postoperative delirium will be classified into three subtypes. Hyperactive delirium will be  
13 defined when the RASS score ranges from 1 to 4; hypoactive delirium will be defined when  
14 the RASS score ranges from -1 to -3, and mixed delirium will be defined when the RASS  
15 score ranges from 1 to 4 and -1 to -3 alternatively. The severity of postoperative delirium  
16 will be rated using the CAM-Severity short-form scale (Supplementary Table 2). Mild-to-  
17 moderate delirium will be defined as a CAM-S score of 3 to 5, while severe delirium will be  
18 defined as a CAM-S score of 6 to 7. [38]

19 Four investigators who are not involved in perioperative care will be responsible for  
20 postoperative delirium assessments and will be trained by a psychiatrist with regard to  
21 symptoms, diagnosis, and treatment of delirium. Furthermore, the psychiatrist will explain  
22 the protocols of 3D-CAM and CAM-ICU in detail, and will perform the simulation training of  
23 delirium assessment until a kappa value over 0.8 is achieved between investigators and  
24 psychiatrists. The training process will be repeated every 4-6 months throughout the study.  
25 In addition, the chart-based delirium identification instrument with the information primarily  
26 derived from electronic medical records system and recalling descriptions of caregivers  
27 will be employed to detect any cases of delirium in patients that may occur outside of in-  
28 person delirium assessments (Supplementary Table 3). [39]

### 29 **Pain and sleep quality measurement**

30 Postoperative pain at rest and during a cough will be evaluated using an 11-point NRS (0

1 = [no pain], 0 < NRS < 4 [mild pain], 4 ≤ NRS < 7 [moderate pain], 7 ≤ NRS < 10 [severe pain], NRS = 10 [worst pain imaginable]. Postoperative sleep quality will also be evaluated using the NRS (0 = best-quality sleep, 10 = worst-quality sleep).

#### 4 **Cognitive function measurement**

5 Postoperative cognitive function will be assessed using the Chinese version of the Telephone Interview for Cognitive Status-40 (TICS-40). The TICS-40 scale used in this study consists of nine items with a maximum score of 40 points, including the following variables and corresponding points: address (3 points), current date (5 points), counting backwards (2 points), word-list recalling (10 points), subtractions (5 points), object naming (2 points), repetition (1 point), the president and prime minister's names (2 points), and delayed recall of the word list (10 points). A score below 21 will be defined as mild cognitive impairment (Supplementary Table 4). [40]

#### 13 **Biomarkers concentration measurement**

14 Venous blood (approximately 6 ml) will be sampled and stored on ice in vacutainer tubes containing EDTA. Within 30 min, the samples will be centrifuged at 4°C for 20 min at 2000× g to obtain plasma and then stored at -80°C. We will measure ACh, BDNF, and TNF-α levels by enzyme-linked immunosorbent assay method (in accordance to manufacturer's instructions). The biomarker assay will be performed by a specialist who is blinded to the randomization. (Supplementary text for the rationales of biomarkers selected)

#### 21 **Adverse events**

22 An adverse event (AE) can be any unfavourable and unintended symptom or side effect temporally associated with the use of study medications. The potential AEs that may be considered in this trial are bradycardia, hypotension, tachycardia, hypertension, arrhythmia, nystagmus, hypersalivation, euphoria, emergence agitation, hallucinations, and nightmares. It is possible, but very unlikely, that low-dose S-ketamine (50 mg in total) administered intraoperatively will cause these psychiatric effects. Potential adverse events and medical rescue are shown in Table 3. [41]

29 Serious AEs are rare, life-threatening events that may be associated with the study drugs or perioperative incidents, such as death or serious cardio-cerebral vascular events.

1

2 **Table 3 The definitions of adverse events and corresponding medication rescue**

Adverse events	Severity	Definition	Treatment
Hypotension (SBP<90 mm Hg or DBP<50 mm Hg or MAP<80% baseline)	Mild	SBP 80-89 mm Hg	Close monitoring
	Moderate	SBP 70-79 mm Hg>2 min	Noradrenaline 4 $\mu\text{g}$ <sup>\$</sup>
	Severe	SBP 60-69 mm Hg>1 min	Noradrenaline 8 $\mu\text{g}$ <sup>#</sup>
	Life-threatening	SBP 60-69 mm Hg and unresponsive to noradrenaline or SBP<60 mm Hg	Intensive intervention and suspend the study
Hypertension (SBP>140 mm Hg or DBP>90 mm Hg or MAP>120% baseline)	Mild	SBP 141-160 mm Hg or DBP 91-100 mm Hg	Close monitoring
	Moderate	SBP 160-170 mm Hg or DBP 101-110 mm Hg >3 min	Urapidil 12.5 mg  Urapidil 25 mg or
	Severe	SBP 171-180 mm Hg or DBP 111-120 mm Hg >2 min	NG 50 $\mu\text{g}$ Intensive intervention and suspend the study
	Life-threatening	SBP>180 mm Hg or DBP>120 mm Hg and unresponsive to NG	
Bradycardia (HR<60 bpm)	Mild	HR 55-60 bpm	Close monitoring
	Moderate	HR 50-54 bpm>3 min	Atropine 0.5 mg
	Severe	HR 40-50 bpm>2 min	Atropine 1.0mg
	Life-threatening	HR<40 bpm and unresponsive to atropine	Intensive intervention and suspend the study
Tachycardia (HR>100 bpm)	Mild	HR 90-100 bpm	Close monitoring
	Moderate	HR 101-110 bpm>3 min	Esmolol 20 mg
	Severe	HR 111-130 bpm>2 min	Esmolol 40 mg
	Life-threatening	HR>130 bpm and unresponsive to Esmolol	Intensive intervention and suspend the study
Hypoxemia (SpO <sub>2</sub> <94%)	Mild	SpO <sub>2</sub> 90%-94%	Close monitoring
	Moderate	SpO <sub>2</sub> 80%-90%>3 min	CPAP
	Severe	SpO <sub>2</sub> 70%-79%>2 min	Two-lung ventilation
	Life-threatening	SpO <sub>2</sub> <70% and unresponsive to two-lung ventilation	Intensive intervention and suspend the study
Emergence delirium	Mild	RASS 1-2	Limb restraint
	Severe	RASS 3-4	Propofol 30 mg
Hallucination/Nystagmus	NA	3D-CAM	Haloperidol 10 mg

3 3D-CAM, 3 minutes diagnostic confusion assessment method; CPAP, constant positive

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4 1 airway pressure; HR, heart rate; NA, not applicable; NG, nitro-glycerine; RASS, Richmond  
5 2 Agitation-Sedation Scale.

6  
7 3 \$ followed by continuous infusion with 0.01-0.1  $\mu\text{g}/\text{kg}/\text{min}$  when necessary

8  
9 4 # followed by continuous infusion with 0.1-0.2  $\mu\text{g}/\text{kg}/\text{min}$  when necessary  
10  
11  
12

### 13 6 **Sample size calculation**

14  
15 7 The sample size was calculated for the main outcome, the incidence of postoperative  
16 8 delirium, using PASS software version 11.0. Based on previous studies and our recently  
17 9 completed data, we estimated that the incidence of POD in elderly patients undergoing  
18 10 non-cardiac thoracic surgery was 40%. [12,42-46] Assuming that dexmedetomidine is  
19 11 associated with a 40% relative reduction in the incidence of postoperative delirium, the  
20 12 non-inferiority margin rate ratio (RR) of S-ketamine versus dexmedetomidine will be set at  
21 13 1.5. [15,27,47,48] To achieve a two-sided type I error of 5% and 80% power, 729  
22 14 participants (243 patients per arm) will be recruited. To accommodate a 5% dropout rate,  
23 15 the final sample size will be 780 (260 patients per arm).  
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### 35 17 **Statistical methods**

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37 18 Kolmogorov-Smirnov test will be used to evaluate the normal distribution of continuous  
38 19 variables. Normally distributed data will be presented as means  $\pm$  standard deviation (SD),  
39 20 and non-normally distributed data will be presented as medians with interquartile ranges.  
40 21 Categorical data will be summarised as counts (proportions).

41  
42 22 The absolute standardised difference (ASD) will be used for the comparison of baseline  
43 23 data among the three groups, that is, the absolute difference in means, mean ranks, or  
44 24 proportions divided by the combined SD. Baseline variables with  $\text{ASD} > 0.013$  (i.e.,  $1.96 \times$   
45 25  $\sqrt{(260 + 260 + 260)/(260 \times 260 \times 260)}$ ) are considered to be imbalanced and will be  
46 26 adjusted for in all analyses when necessary.

47  
48 27 For the primary outcome, the incidence of postoperative delirium, the intention-to-treat  
49 28 approach and per-protocol (PP) approach will be performed. Pearson's chi-square test will  
50 29 be applied to compare proportions with the primary outcome among groups. The difference  
51 30 among groups will be expressed as RR and 95% confidence interval (CI), while non-



1 inferiority will be identified if the upper limit of 95% CI of RR is  $< 1.5$ . For the secondary  
2 outcomes, only the PP approach will be used. Normally distributed data will be analysed  
3 with one-way analysis of variance (ANOVA); Non-normally distributed data will be  
4 analysed with Kruskal-Wallis test. The median difference will be calculated using the  
5 Hodges-Lehmann estimation on the basis of the Kruskal-Wallis test. Adverse events that  
6 are presented as incidences will be compared by calculating the 95% CI of the incidence  
7 difference: incidence (S group) – incidence (D group), and noninferiority will be achieved  
8 if the upper limit of 95% CI is  $< 5\%$ . The superiority for outcomes will be assessed when  
9 noninferiority is verified.

10 To account for correlation among repeated measurements, such as numeric rating  
11 scores for pain and sleep quality, plasma biomarker concentrations, and cognitive function,  
12 will be compared using generalised estimating equation analysis among groups. The time  
13 to delirium will be calculated with the Kaplan-Meier estimator, and the differences among  
14 groups will be assessed by the log-rank test. The number needed to treat will be estimated  
15 for the primary outcome.

16 Missing values will be adjusted using random forest imputation in the missForest  
17 package. However, missing values, due to fatigue in the assessment or the patient's  
18 inability to cooperate, will be imputed with positive results or means in the corresponding  
19 treatment group and time point. If the patient did not have a delirium assessment at all (e.g.  
20 dropout or death), no values will be imputed. The last assessment is used to replace the  
21 missing value to estimate the incidence of postoperative delirium in patients who are  
22 discharged or die within 4 days, while the missing value of assessment per day does not  
23 need to be replaced.

24 The *P* values and CIs reported from one-way ANOVA and Kruskal-Wallis test will be  
25 considered to illustrate statistical significance if they are less than 0.017 and 98.3%,  
26 respectively, accounting for three pairwise comparisons. The family-wise significance and  
27 CI levels among the three groups will be set at 0.05% and 95%, respectively. For the pain  
28 intensity score, a 1.1 decrease will be considered the minimal clinically important difference.  
29 [49]

30 Analyses will be conducted using IBM SPSS version 25.0 (SPSS Software, Chicago,

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4 1 IL, USA), R statistics version 4.1.2 (R Project for Statistical Computing), and GraphPad  
5 2 Prism version 8.0 (GraphPad Software, San Diego, CA, USA).  
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8 3

#### 4 **Ethics and confidentiality**

5 Ethical approval was obtained from the Institutional Review Board of the Cancer Hospital  
6 and the Institute of Guangzhou Medical University (ZN202119). The study has also been  
7 registered at Chictr.org.cn with the identifier ChiCTR2100052750. The personal  
8 information of the participants will not be disclosed unless authorisation is approved. In  
9 addition, each participant will be provided with a unique identity code, the information of  
10 which will be properly secured. The CRF and Epidata database will be retained for a  
11 minimum of 10 years.  
12

#### 13 **Patient and Public Involvement**

14 No patients or public representatives were involved in the design of this trial.  
15

#### 16 **Dissemination**

17 At the end of the trial, we commit to making public disclosure available despite the outcome.  
18 Public disclosure will include publication in an appropriate journal or oral presentation at  
19 an academic meeting. The PI will be considered the first or corresponding author. The  
20 investigators who contribute a minimum of four months to the trial will be co-authors;  
21 otherwise, they will be acknowledged in the publication.  
22

#### 23 **Discussion**

24 Lung cancer ranks first among all malignancies in China, and anatomic pulmonary  
25 resection is a major component of multimodal therapy according to the lung cancer  
26 guidelines. [12] However, more than 40% of patients undergoing lung cancer surgery are  
27 inflicted by severe depression-related psychological suffering postoperatively. [50]  
28 Depression is an independent predictor of postoperative delirium in patients who undergo  
29 orthopaedic and cancer surgeries. [24] Based on its pharmacological mechanisms and  
30 antidepressant effects, we speculate that S-ketamine would be non-inferior to

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4 1 dexmedetomidine in reducing postoperative delirium to some extent in the elderly, with  
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6 2 fewer episodes of hypotension or less opioid consumption. Hypotension is pertinent to  
7  
8 3 delirium, and minimisation of intraoperative hypotension episodes is recommended to  
9  
10 4 reduce postoperative delirium. [51] Additionally, the administration of opioids (long-acting  
11  
12 5 opioids in particular) is closely related to postoperative delirium in a dose-dependent  
13  
14 6 manner. Hence, it is critical to abate opioid consumption in order to curtail delirium. [8]

15  
16 7 Although previous studies have demonstrated that ketamine failed to reduce the  
17  
18 8 incidence of postoperative delirium in patients undergoing major cardiac or non-cardiac  
19  
20 9 surgery, we will deploy a different administrative protocol to evaluate the effect of an isomer  
21  
22 10 of ketamine on postoperative delirium accompanied by dexmedetomidine as a positive  
23  
24 11 comparator and by an optimal sample size. Dexmedetomidine is a highly recommended  
25  
26 12 agent in the prevention and treatment of postoperative delirium; however, it is commonly  
27  
28 13 accompanied by hypotension and bradycardia in the elderly. As the prevention of  
29  
30 14 postoperative delirium is more practical and effective than the treatment itself, creating a  
31  
32 15 means of prevention for delirium is extraordinarily indispensable. We believe that the  
33  
34 16 possible result will be one of the following: (1) S-ketamine will be non-inferior to  
35  
36 17 dexmedetomidine in the prevention of postoperative delirium; meanwhile, more stable  
37  
38 18 haemodynamics, lower postoperative pain severity, or other beneficial secondary  
39  
40 19 outcomes will be observed with S-ketamine intervention. Side effects will be compared  
41  
42 20 between groups, all of which will be our desirables. This suggests that S-ketamine will be  
43  
44 21 an optimal choice for limiting delirium emergence in the elderly, and further studies should  
45  
46 22 be performed to evaluate its effect on long-term cognitive function. (2) S-ketamine will be  
47  
48 23 non-inferior to dexmedetomidine in postoperative delirium prevention with comparable  
49  
50 24 secondary outcomes; however, it will be accompanied by frequent side effects. This  
51  
52 25 indicates that S-ketamine will be clinically valueless for delirium prevention, which is also  
53  
54 26 possible in view of the results from previous studies on ketamine (PODCAST and PRIDe  
55  
56 27 study). (3) S-ketamine will be inferior to dexmedetomidine in the prevention of  
57  
58 28 postoperative delirium, which is probably because dexmedetomidine is recognised as the  
59  
60 29 most effective medication for delirium, and fewer studies have compared the two drugs.

30 The SKED protocol has many limitations. First, the current trial is launched at special

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3  
4 1 time when inclusion may be constrained by local SARS-CoV-2 pandemic. As such, the  
5  
6 2 research period may take longer than anticipated. Second, this is a single-centre study  
7  
8 3 that exclusively involves thoracic surgery; therefore, the generalisability may not be  
9  
10 4 extrapolated. Third, an anticipated non-inferiority margin ratio of 1.5 in our trial may be  
11  
12 5 too large, and consequently, the sample size may be underestimated. Fourth, a dropout  
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14 6 rate of 5% seems a bit low as adverse events due to dexmedetomidine may be higher than  
15  
16 7 that, if so, we would enlarge the sample size upon approval from the IRB.  
17  
18 8

19 9 **Authors' contributions** Wei Wei, Anyu Zhang, Xi Zheng, Ming Zhou, and Yonghua Yao  
20  
21 10 participated in the study design. Wei Wei, Anyu Zhang, and Xi Zheng co-drafted the  
22  
23 11 protocol manuscript. Yu Gu and Yonghua Yao contributed to sample size calculation and  
24  
25 12 statistical consultation. Wei Wei and Xi Zheng developed the case report forms and the  
26  
27 13 Epidata database. Wei Wei, Lv Liu, and Chunlin Tang conducted the preliminary trial.  
28  
29 14 Yonghua Yao served as the primary investigator and provided the funding. All authors  
30  
31 15 completed 3D-CAM and CAM-ICU training courses and obtained good clinical practice  
32  
33 16 certificates.

34  
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47  
48 23 **Competing interests statement:** All authors have no conflicts of interest to declare.

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51 24 **Patient consent for publication:** Consent obtained directly from patients.

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54 25 **Provenance and peer review:** Not commissioned; externally peer-reviewed.  
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## 20 **Figure legends**

21 **Figure 1.** Consolidated Standards of Reporting Trials (CONSORT) flow diagram.

22 **Figure 2.** Overview of 3-minute Diagnostic Confusion Assessment Method (3D-CAM)  
23 assessment.

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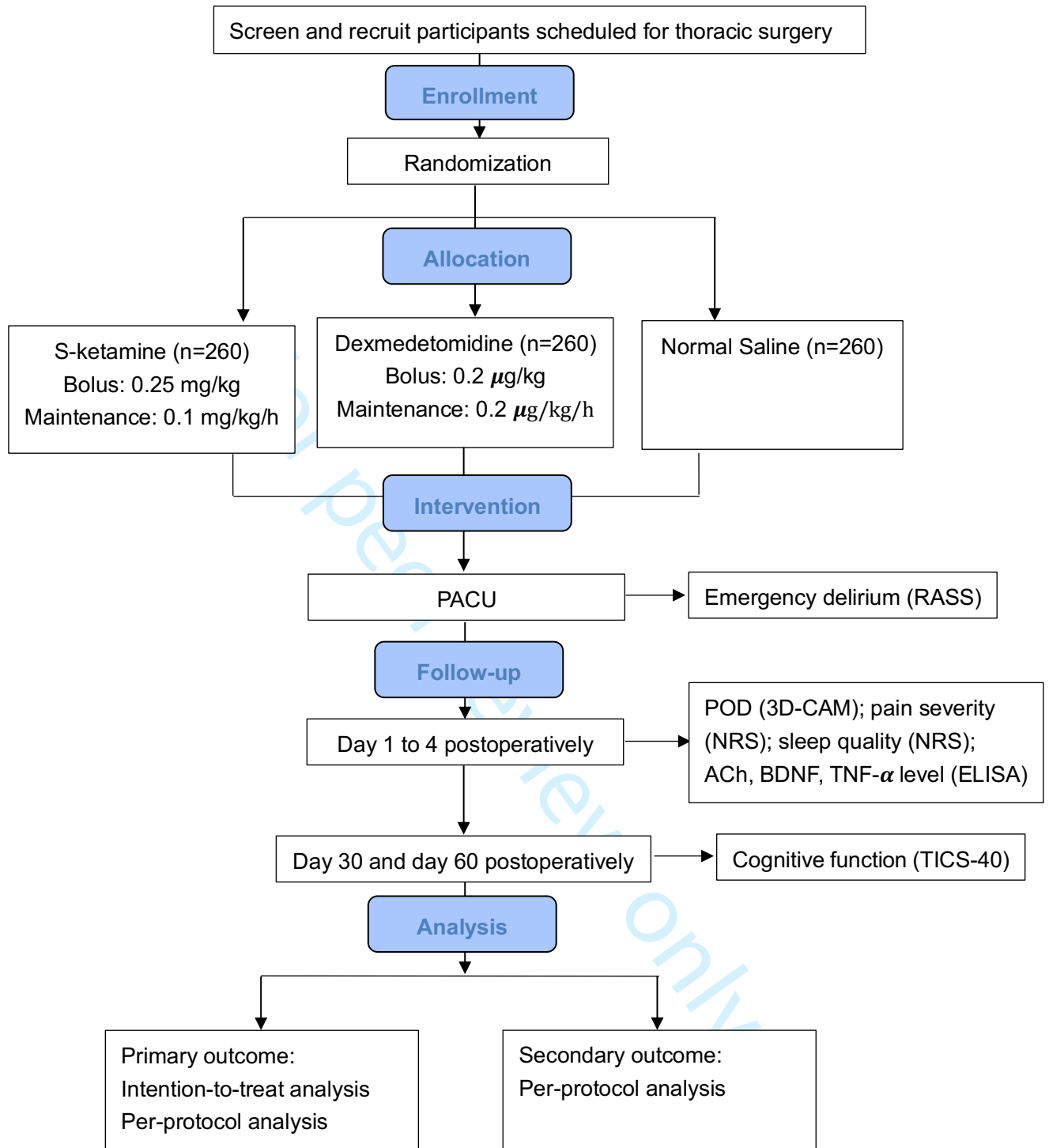
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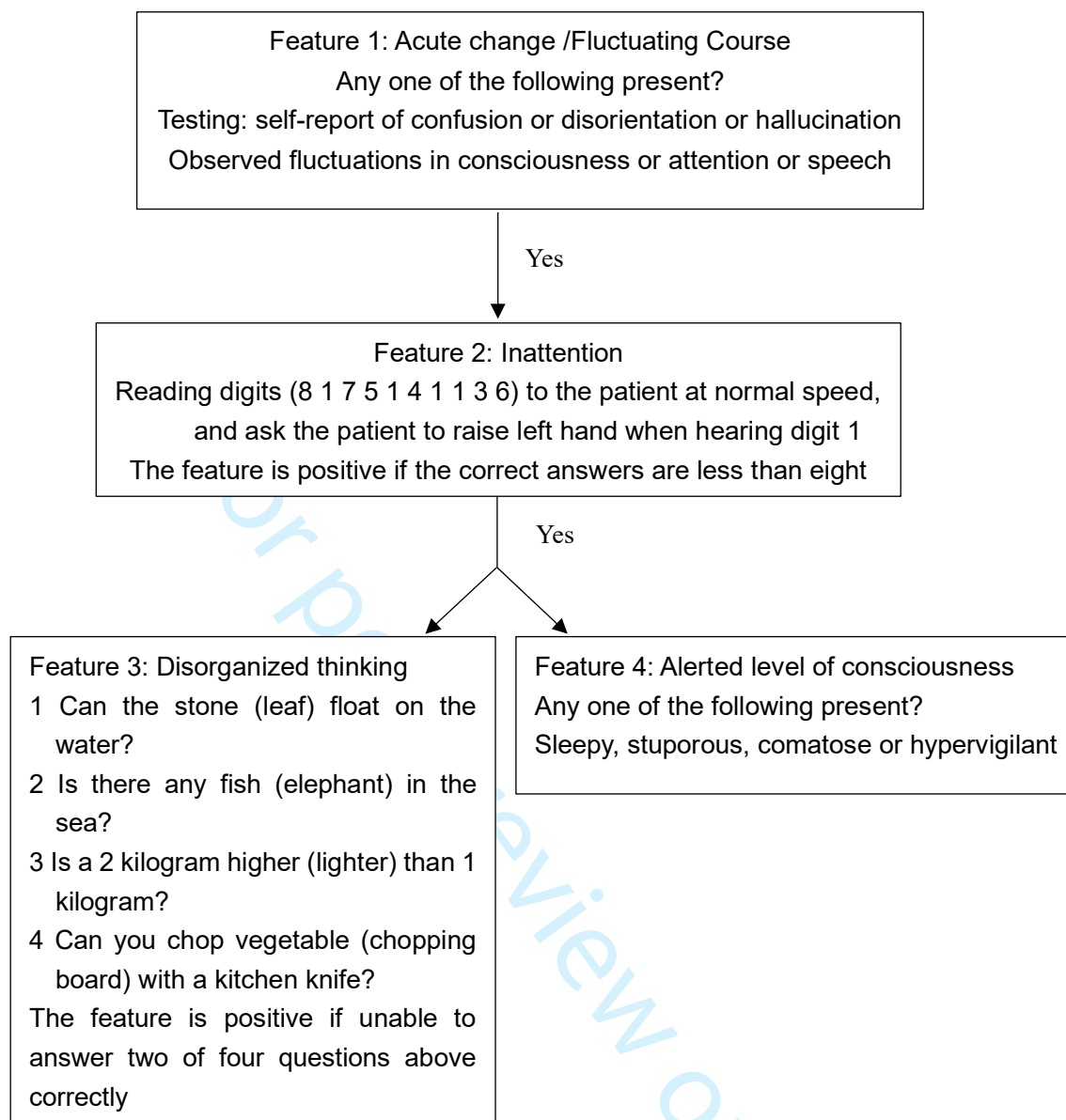
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For peer review only



**Figure 1.** Consolidated Standards of Reporting Trials (CONSORT) flow diagram



**Figure 2.** Overview of 3-minute diagnostic confusion assessment method (3D-CAM) assessment.

Supplementary table 1 Richmond agitation-sedation scale

Score	Term	Description
+4	Combative	Overtly combative or violate; immediate danger to staff
+3	Very agitated	Pulls on 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 (>10 seconds) awakening (eye-opening/eye contact) to voice
-2	Light sedation	Briefly (<10 seconds) awakens with eye contact to voice
-3	Moderate sedation	Movement or eye opening (but no eye contact) to voice
-4	Deep sedation	No response to voice, but any movement to physical stimulation
-5	Unarousable	No response to voice or physical stimulation

Supplementary table 2 CAM-S short form scale\*

Feature	Severity Score		
	Not Present	Present (mild)	Present (marked)
Acute onset & fluctuation course	0	1	—
Inattention	0	1	2
Disorganized thinking	0	1	2
Altered level of consciousness	0	1	2

\*: Rate each symptom of delirium listed in the 3D-CAM as absent (0), mild (1), marked (2). Acute onset & fluctuation course is rated as absent (0) or present (1). Add these scores into a composite. Higher scores indicate more severe delirium.

Supplementary table 3 Chart-based delirium identification instrument

Question	Circle answer
Is there any evidence in the chart of acute confusion (e.g., delirium, mental status change, disorientation, hallucinations, agitation etc.)? Review entire medical record, including progress notes, nursing notes, consult notes, etc.	Yes No Uncertain
What is the source of information about the first episode of acute confusion?	Nurse's notes Physician's notes Other (specify): _____
Approximate time of onset first episode of acute confusion? Check nurse's notes, progress notes, orders, laboratories, for the earliest time referable to the event.	Date: ___ / ___ / ___ Month Day Year Time: ___ : ___ am/pm Uncertain

Supplementary table 4 Telephone interview for cognitive status-40 (TICS-40) instrument  
Chinese version

Item	Score
What is today's date?	5
What is your address?	3
Counting backwards from 20 to 1	2
Repeating following 10 words: ball, flag, woods, watch, television, cellphone, scissor, pillow, pen, whip	10
Subtracting 7 from 100, 93, 86, 79, 72, 65	5
What do people usually use to cut paper?	2
Say this "no pains, no gains"	1
President's and prime minister's name	2
Recalling 10 words above mentioned	10

## Supplementary

The rationales for the biomarkers selected

### 1. The rational for the choice of TNF- $\alpha$

Surgery activates the innate immune system resulting in release of proinflammatory mediators (TNF- $\alpha$ , IL-1 and IL-6). However, ketamine could suppress nuclear factor- $\kappa$ B expression involved in the transcription of genes encoding the proinflammatory cytokines tumour necrosis factor (TNF- $\alpha$ ). [1]

### 2. The rational for the choice of BDNF

BDNF has a role in increasing synaptic plasticity and synaptic function. Reviews have suggested that brain-derived neurotrophic factor (BDNF) improved memory function, reversed age-related changes in brain and prevented cell death. [2] Furthermore, ketamine requires brain-derived neurotrophic factor (BDNF) signals to exert antidepressant effects. [3]

### 3. The rational for the choice of acetylcholine

Acetylcholine is thought to be involved in the neuroplasticity, and is present in several neural pathways responsible for arousal, attention and memory. [4] However, ketamine could increase cholinergic tone that may contribute to the improvement of cognition. [5]

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# Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

## Instructions to authors

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Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

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		Reporting Item	Page Number
<b>Administrative information</b>			
Title	<a href="#">#1</a>	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	<a href="#">#2a</a>	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	<a href="#">#2b</a>	All items from the World Health Organization Trial Registration Data Set	
Protocol version	<a href="#">#3</a>	Date and version identifier	6
Funding	<a href="#">#4</a>	Sources and types of financial, material, and other support	21
Roles and responsibilities: contributorship	<a href="#">#5a</a>	Names, affiliations, and roles of protocol contributors	1,20



1	Roles and	<a href="#">#5b</a>	Name and contact information for the trial sponsor	1
2	responsibilities:			
3	sponsor contact			
4	information			
5				
6				
7				
8	Roles and	<a href="#">#5c</a>	Role of study sponsor and funders, if any, in study design;	20
9	responsibilities:		collection, management, analysis, and interpretation of data;	
10	sponsor and funder		writing of the report; and the decision to submit the report for	
11			publication, including whether they will have ultimate	
12			authority over any of these activities	
13				
14				
15				
16	Roles and	<a href="#">#5d</a>	Composition, roles, and responsibilities of the coordinating	
17	responsibilities:		centre, steering committee, endpoint adjudication committee,	
18	committees		data management team, and other individuals or groups	
19			overseeing the trial, if applicable (see Item 21a for data	
20			monitoring committee)	
21				
22				
23				
24	<b>Introduction</b>			
25				
26				
27	Background and	<a href="#">#6a</a>	Description of research question and justification for	3
28	rationale		undertaking the trial, including summary of relevant studies	
29			(published and unpublished) examining benefits and harms	
30			for each intervention	
31				
32				
33				
34	Background and	<a href="#">#6b</a>	Explanation for choice of comparators	4,5
35	rationale: choice of			
36	comparators			
37				
38				
39	Objectives	<a href="#">#7</a>	Specific objectives or hypotheses	5,6
40				
41	Trial design	<a href="#">#8</a>	Description of trial design including type of trial (eg, parallel	6
42			group, crossover, factorial, single group), allocation ratio, and	
43			framework (eg, superiority, equivalence, non-inferiority,	
44			exploratory)	
45				
46				
47				
48	<b>Methods:</b>			6
49	<b>Participants,</b>			
50	<b>interventions, and</b>			
51	<b>outcomes</b>			
52				
53				
54				
55	Study setting	<a href="#">#9</a>	Description of study settings (eg, community clinic, academic	6
56			hospital) and list of countries where data will be collected.	
57			Reference to where list of study sites can be obtained	
58				
59				
60				

1	Eligibility criteria	<a href="#">#10</a>	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7-8
2				
3				
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5				
6	Interventions:	<a href="#">#11a</a>	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	11
7	description			
8				
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10				
11	Interventions:	<a href="#">#11b</a>	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)	15
12	modifications			
13				
14				
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18	Interventions:	<a href="#">#11c</a>	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	
19	adherence			
20				
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23				
24	Interventions:	<a href="#">#11d</a>	Relevant concomitant care and interventions that are permitted or prohibited during the trial	8
25	concomitant care			
26				
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28	Outcomes	<a href="#">#12</a>	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	12,13
29				
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38				
39	Participant timeline	<a href="#">#13</a>	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	6,7
40				
41				
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44				
45				
46	Sample size	<a href="#">#14</a>	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	16
47				
48				
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51				
52	Recruitment	<a href="#">#15</a>	Strategies for achieving adequate participant enrolment to reach target sample size	6
53				
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55				

## Methods:

### Assignment of

1 **interventions (for**  
2 **controlled trials)**

3			
4	Allocation: sequence	<a href="#">#16a</a>	Method of generating the allocation sequence (eg, computer-
5	generation		generated random numbers), and list of any factors for
6			stratification. To reduce predictability of a random sequence,
7			details of any planned restriction (eg, blocking) should be
8			provided in a separate document that is unavailable to those
9			who enrol participants or assign interventions
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14	Allocation	<a href="#">#16b</a>	Mechanism of implementing the allocation sequence (eg,
15	concealment		central telephone; sequentially numbered, opaque, sealed
16	mechanism		envelopes), describing any steps to conceal the sequence until
17			interventions are assigned
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21	Allocation:	<a href="#">#16c</a>	Who will generate the allocation sequence, who will enrol
22	implementation		participants, and who will assign participants to interventions
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24	Blinding (masking)	<a href="#">#17a</a>	Who will be blinded after assignment to interventions (eg,
25			trial participants, care providers, outcome assessors, data
26			analysts), and how
27			
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30	Blinding (masking):	<a href="#">#17b</a>	If blinded, circumstances under which unblinding is
31	emergency unblinding		permissible, and procedure for revealing a participant's
32			allocated intervention during the trial
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35	<b>Methods: Data</b>		
36	<b>collection,</b>		
37	<b>management, and</b>		
38	<b>analysis</b>		
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42	Data collection plan	<a href="#">#18a</a>	Plans for assessment and collection of outcome, baseline, and
43			other trial data, including any related processes to promote
44			data quality (eg, duplicate measurements, training of
45			assessors) and a description of study instruments (eg,
46			questionnaires, laboratory tests) along with their reliability
47			and validity, if known. Reference to where data collection
48			forms can be found, if not in the protocol
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53	Data collection plan:	<a href="#">#18b</a>	Plans to promote participant retention and complete follow-
54	retention		up, including list of any outcome data to be collected for
55			participants who discontinue or deviate from intervention
56			protocols
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1	Data management	<a href="#">#19</a>	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	12-13
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9	Statistics: outcomes	<a href="#">#20a</a>	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	16,17,18
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14	Statistics: additional analyses	<a href="#">#20b</a>	Methods for any additional analyses (eg, subgroup and adjusted analyses)	
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18	Statistics: analysis population and missing data	<a href="#">#20c</a>	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	17
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24	<b>Methods:</b>			
25	<b>Monitoring</b>			
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27	Data monitoring: formal committee	<a href="#">#21a</a>	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	20
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37	Data monitoring: interim analysis	<a href="#">#21b</a>	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	
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43	Harms	<a href="#">#22</a>	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	15-16
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48	Auditing	<a href="#">#23</a>	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	
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53	<b>Ethics and dissemination</b>			
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57	Research ethics approval	<a href="#">#24</a>	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	2
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1	Protocol amendments	<a href="#">#25</a>	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)	
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8	Consent or assent	<a href="#">#26a</a>	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8
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13	Consent or assent: ancillary studies	<a href="#">#26b</a>	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	
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18	Confidentiality	<a href="#">#27</a>	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	19
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24	Declaration of interests	<a href="#">#28</a>	Financial and other competing interests for principal investigators for the overall trial and each study site	21
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27	Data access	<a href="#">#29</a>	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	13
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33	Ancillary and post trial care	<a href="#">#30</a>	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	
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38	Dissemination policy: trial results	<a href="#">#31a</a>	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	2
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46	Dissemination policy: authorship	<a href="#">#31b</a>	Authorship eligibility guidelines and any intended use of professional writers	2
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50	Dissemination policy: reproducible research	<a href="#">#31c</a>	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	2
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54	<b>Appendices</b>			
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56	Informed consent materials	<a href="#">#32</a>	Model consent form and other related documentation given to participants and authorised surrogates	supplemental
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1 Biological specimens [#33](#) Plans for collection, laboratory evaluation, and storage of 15  
2 biological specimens for genetic or molecular analysis in the  
3 current trial and for future use in ancillary studies, if  
4 applicable  
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10 tool made by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)  
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