

# BMJ Open Effect of balanced opioid-free anaesthesia on postoperative nausea and vomiting after video-assisted thoracoscopic lung resection: protocol for a randomised controlled trial

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## ABSTRACT

**Introduction** Opioid-free anaesthesia (OFA) may reduce opioid-related side effects such as postoperative nausea and vomiting (PONV) and hyperalgesia. This study aims to investigate the effects of balanced OFA on PONV and pain outcomes in patients undergoing video-assisted thoracoscopic surgery (VATS).

**Methods and analysis** This randomised controlled trial will be conducted at the First Affiliated Hospital of Soochow University in Suzhou, China. A total of 120 adults scheduled for VATS lung resection will be randomly assigned with a 1:1 ratio to either an OFA group or a control group, stratified by sex (n=60 in each group). Patients will receive balanced anaesthesia with esketamine, dexmedetomidine and sevoflurane (the OFA group), or sufentanil and sevoflurane (the control group). All patients will receive PONV prophylaxis with intraoperative dexamethasone and ondansetron. Multimodal analgesia consists of intraoperative flurbiprofen axetil, ropivacaine infiltration at the end of surgery and postoperative patient-controlled sufentanil. The primary outcome is the incidence of PONV within 48 hours after surgery. Secondary outcomes are nausea, vomiting, need for antiemetic therapy, pain scores at rest and while coughing, postoperative sufentanil consumption, need for rescue analgesia, length of post-anaesthesia care unit stay, length of postoperative hospital stay, and 30-day and 90-day post-surgical pain and mortality. Safety outcomes are hypotension, bradycardia, hypertension, tachycardia, interventions for haemodynamic events, level of sedation, headache, dizziness, nightmare and hallucination. All analyses will be performed in the modified intention-to-treat population.

**Ethics and dissemination** Ethics approval was obtained from the Ethics Committee of the First Affiliated Hospital of Soochow University (2022-042). All patients will provide written informed consent. The results of this study will be published in a peer-reviewed journal.

**Trial registration number** Chinese Clinical Trial Registry (ChiCTR2200059710).

## INTRODUCTION

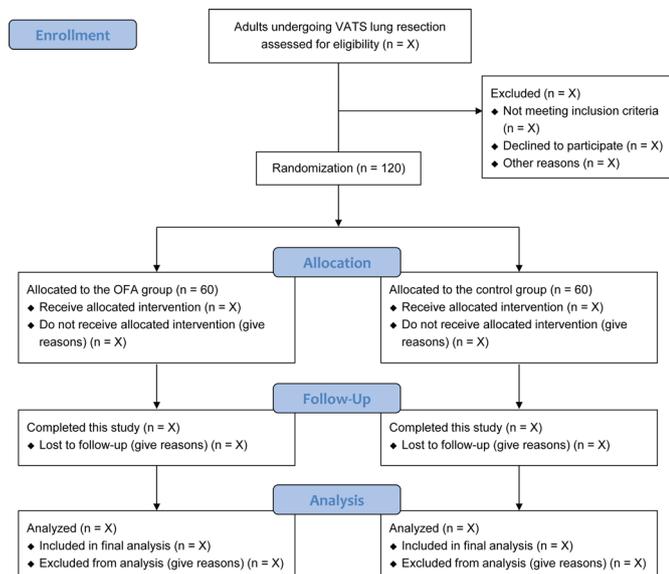
Video-assisted thoracoscopic surgery (VATS) has been increasingly performed over the

## STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ The Apfel's postoperative nausea and vomiting risk scores will be calculated preoperatively, based on the number of risk factors.
- ⇒ Anaesthesia depth will be titrated to bispectral index values of 40–60 in both groups.
- ⇒ 3. All patients will receive perioperative multimodal analgesia (flurbiprofen axetil, ropivacaine infiltration and patient-controlled sufentanil).
- ⇒ Anaesthesia providers cannot be blinded due to the differences between techniques, but they will not participate in other parts of the study.
- ⇒ This is a single-centre trial, and more studies evaluating opioid-free anaesthesia will be warranted.

decades, with less postoperative pain and faster recovery compared with thoracotomy.<sup>1</sup> Postoperative nausea and vomiting (PONV) are common for patients undergoing VATS, and moderate to severe pain after VATS is not rare.<sup>2</sup> PONV and postoperative pain are associated with increased healthcare costs and decreased quality of life after surgery.<sup>3,4</sup>

Opioids are regarded as the cornerstone of analgesia for patients undergoing surgery. However, use of opioids is associated with increased risks of PONV and hyperalgesia (paradoxical increases in pain and opioid requirements).<sup>5,6</sup> To overcome these, opioid-free anaesthesia (OFA) appears to be an interesting alternative. OFA is commonly delivered using intravenous dexmedetomidine, ketamine or esketamine, and lidocaine, together with multimodal analgesia (non-steroid anti-inflammatory drugs, nerve blocks or local anaesthetic wound infiltration).<sup>7,8</sup> Previous reports suggested that OFA was associated with decreased PONV and opioid consumption,<sup>9,10</sup> but recent studies did not support that association.<sup>11,12</sup> The



**Figure 1** Study flow diagram. OFA, opioid-free anaesthesia; VATS, video-assisted thoracoscopic surgery.

anaesthetic and analgesic components of OFA vary among different institutions, and the benefits as well as potential risks of OFA for surgical patients remain inconclusive.

## Objectives

This study aims to compare a balanced OFA versus a balanced opioid-based anaesthesia for patients undergoing VATS lung resection. We hypothesise that our OFA regimen would reduce PONV and improve postoperative pain outcomes after VATS lung procedures.

## METHODS AND ANALYSIS

The reporting of this protocol follows the guidelines of Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) (online supplemental file 1).<sup>13</sup>

### Study design and patients

This is a single-centre, prospective, randomised, patient-blind and assessor-blind, parallel-group controlled, superiority clinical trial. A total of 120 patients will be enrolled at the First Affiliated Hospital of Soochow University in Suzhou, China. The First Affiliated Hospital of Soochow University is a tertiary teaching hospital at which approximately 4000 VATS procedures are performed each year. We plan to enrol patients between 18 May 2022 and 30 November 2022. The study flow diagram is presented in figure 1.

### Inclusion criteria

To be included in this study, patients should meet the following criteria:

1. Age  $\geq 18$  years.
2. American Society of Anesthesiologists (ASA) physical status I–III.
3. Body mass index (BMI) 18–30 kg/m<sup>2</sup>.
4. Scheduled for elective VATS lung resection.

### Exclusion criteria

The exclusion criteria are as follows:

1. Sick sinus syndrome or severe bradycardia (heart rate (HR) <50 beats/min).
2. Second-degree or greater atrioventricular block without a pacemaker.
3. Left ventricular ejection fraction <40%.
4. Coronary heart disease or history of myocardial infarction.
5. Liver or renal dysfunction (Child-Pugh class C or undergoing renal replacement therapy).
6. Parkinson's disease or Alzheimer's disease.
7. Seizures or epilepsy.
8. Pregnancy or breast feeding.
9. History of chronic pain or preoperative use of sedatives or analgesics.
10. Allergies to medications in this study.

### Apfel's PONV risk scores

The Apfel's PONV risk scores will be calculated preoperatively, based on the number of risk factors (female, non-smoker, history of PONV or motion sickness, and postoperative use of opioids).<sup>14</sup> The Apfel's PONV risk scores range from 0 to 4, with each point predicting a 20% increased risk of developing PONV.<sup>14</sup>

### Randomisation and blinding

An independent research personnel will generate the random numbers using the online tool (<https://www.sealedenvelope.com/simple-randomiser/v1/lists>), with a 1:1 allocation ratio, permuted blocks of 2 and 4, and stratification by sex. The randomisation results will be stored in sealed opaque envelopes. Patients will be randomly assigned to either an OFA group or an opioid-based control group (n=60 in each arm). The anaesthesia providers cannot be blinded to the group allocation due to the differences between the anaesthesia techniques; however, they will not participate in patient recruitment, data collection or statistical analysis. Patients, surgeons, postoperative care providers, outcome assessors and a statistician responsible for analyses will be masked to the group allocation.

### Study interventions

For induction of anaesthesia, the OFA group will receive intravenous dexmedetomidine 0.6 µg/kg over 10 min, esketamine 0.3 mg/kg and propofol 1.5–2.0 mg/kg; the control group will receive intravenous sufentanil 0.3 µg/kg and propofol 1.5–2.0 mg/kg. For maintenance of anaesthesia, the OFA group will receive dexmedetomidine infusion at 0.2–1.0 µg/kg/hour, 1%–3% sevoflurane inhalation and boluses of esketamine 0.1 mg/kg; the control group will receive 1%–3% sevoflurane inhalation and boluses of sufentanil 0.1 µg/kg. The schedule of patient enrolment, study interventions and outcome assessment is in accordance with the SPIRIT statement (table 1).

**Table 1** Schedule of patient enrolment, study interventions and outcome assessment

Time point	Study period							
	Enrolment	Allocation	Post-allocation				Close-out	Follow-up
	Preoperative visit	2 hours before surgery	Intraoperatively	PACU	24 hours postoperatively	48 hours postoperatively	Hospital discharge	30 and 90 days
Patient enrolment								
Eligibility criteria	x							
Written informed consent	x							
Demographic data	x							
Baseline characteristics	x							
Randomisation/ allocation		x						
Study interventions								
Opioid-free anaesthesia			x					
Opioid-based anaesthesia			x					
Outcome assessment								
PONV				x	x		x	
Need for antiemetics				x	x		x	
Postoperative pain scores				x	x		x	
Postoperative sufentanil consumption				x	x		x	
Need for rescue analgesia				x	x		x	
Length of PACU stay				x				
Length of hospital stay							x	
30-day and 90-day post-surgical pain								x
30-day and 90-day mortality								x
Hypotension			x	x				
Hypertension			x	x				
Bradycardia			x	x				
Tachycardia			x	x				
Interventions for haemodynamic events			x	x				
Level of sedation				x				
Headache				x	x		x	
Dizziness				x	x		x	
Nightmare				x	x		x	
Hallucination				x	x		x	

According to SPIRIT statement of defining standard protocol items for clinical trials.

PACU, post-anaesthesia care unit; PONV, postoperative nausea and vomiting; SPIRIT, Standard Protocol Items: Recommendations for Interventional Trials.

## Anaesthetic care

Patients will fast for 6–8 hours. No premedication will be given. In a preoperative waiting room, the baseline blood pressure and HR will be obtained. In the operating room, patients will receive continuous monitoring with ECG, non-invasive blood pressure, pulse oximetry (SpO<sub>2</sub>) and bispectral index (BIS) (Aspect Medical Systems, Newton, Massachusetts, USA).

After anaesthesia induction, a catheter will be inserted into the radial artery for arterial blood pressure monitoring. Rocuronium 0.6 mg/kg will be administered to facilitate the intubation of a double-lumen endotracheal tube. The location of the tube will be confirmed by capnography, auscultation and fiberoptic bronchoscopy. One-lung mechanical ventilation will be started on the non-surgical side with tidal volume of 6–8 mL/kg (predicted body weight) and positive end-expiratory pressure of 5–10 cm H<sub>2</sub>O. The inspired oxygen fraction and respiratory frequency will be adjusted to maintain SpO<sub>2</sub> ≥95% and end-tidal carbon dioxide within 35–45 mm Hg. Lung recruitment manoeuvres will be applied when clinically indicated.

Anaesthesia depth will be titrated to BIS values of 40–60 via adjusting inhalational sevoflurane concentration. Sufficient intraoperative analgesia will be provided via adjusting the infusion rate of dexmedetomidine and using boluses of esketamine (the OFA group) or boluses of sufentanil (the control group), at the discretion of the attending anaesthesiologist. For intraoperative muscle relaxation, patients will receive additional rocuronium administration. Patients will receive Lactated Ringer's solution for intravenous fluid repletion. A warming blanket will be used to maintain the nasopharyngeal temperature at 36°C–37°C. After surgery, all patients will be transferred to the post-anaesthesia care unit (PACU). The Modified Observer's Alertness/Sedation Scale (MOAA/S) and modified Aldrete score will be assessed every 5 min.<sup>15 16</sup> A modified Aldrete score ≥9 indicates readiness for PACU discharge to surgical wards.<sup>17</sup>

All patients will receive PONV prophylaxis using intravenous dexamethasone 5 mg and ondansetron 4 mg during anaesthesia. If patients experience vomiting in the PACU and surgical wards, they will receive an additional administration of ondansetron 4 mg as antiemetic therapy.

For multimodal analgesia, the patients in both groups will receive intraoperative flurbiprofen axetil 50 mg, wound infiltration with 0.5% ropivacaine 20 mL at the end of surgery and postoperative patient-controlled sufentanil until 48 hours postoperatively. The patient-controlled analgesia (PCA) device contains sufentanil 100 µg diluted with normal saline to a total volume of 100 mL (ie, sufentanil 1 µg/mL), with a background infusion of 1 mL/hour, a bolus dose of 2 mL and a lockout time of 10 min. Postoperative pain will be assessed using the Numerical Rating Scale, ranging from 0 to 10 (0=no pain and 10=the worst pain imaginable). If pain scores remain ≥4 despite the use of patient-controlled sufentanil, rescue analgesia with additional intravenous sufentanil 5 µg will be given.

## Primary and secondary outcomes

The primary outcome of this trial is the incidence of PONV during the first 48 hours postoperatively. We will assess PONV as the combined incidence of nausea, retching and vomiting. The secondary outcomes are nausea, vomiting, need for antiemetic therapy, pain scores at rest and while coughing, postoperative sufentanil consumption, need for rescue analgesia, length of PACU stay, length of postoperative hospital stay, and 30-day and 90-day post-surgical pain and mortality.

Nausea, vomiting, need for antiemetic therapy and need for rescue analgesia will be recorded within 48 hours postoperatively. Postoperative pain scores at rest and while coughing and postoperative sufentanil consumption will be recorded at PACU discharge and 24 and 48 hours postoperatively. Follow-up data on post-surgical pain and mortality will be collected via telephone calls at 30 and 90 days after surgery.

## Safety outcomes

The safety outcomes include perioperative hypotension (reduction in mean blood pressure >30% of baseline for at least 1 min),<sup>18</sup> bradycardia (HR <45 beats/min for at least 1 min), hypertension (increase in mean blood pressure >30% of baseline for at least 1 min), tachycardia (HR >100 beats/min for at least 1 min), interventions for haemodynamic events, MOAA/S sedation levels, headache, dizziness, nightmare and hallucination. These haemodynamic events will be assessed during anaesthesia and in the PACU, and interventions will be at the discretion of the attending anaesthesiologist, via adjusting dexmedetomidine infusion, using additional esketamine or sufentanil, and using intravenous vasopressors (ephedrine 6–10 mg or phenylephrine 50–100 µg), atropine 0.3–0.5 mg, urapidil 5 mg or esmolol 10 mg, as appropriate. The episodes of headache, dizziness, nightmare and hallucination within 48 hours postoperatively will be recorded.

## Data collection and monitoring

An independent research staff will collect demographic data (age, sex, height, weight and BMI), baseline characteristics (preoperative medications, comorbidities, ASA physical status, smoking status, education level and Apfel's PONV risk score) and perioperative data (BIS values, haemodynamic data, end-tidal sevoflurane concentration, and doses of propofol, sufentanil, esketamine, dexmedetomidine, and all other medications). All data will be collected in the case report forms and then entered into the electronic database under the supervision of the principal investigator (KP). An independent data monitoring committee (DMC) will conduct an ongoing review of data collection. The electronic database will be locked once the data registration is completed. Datasets without personally identifiable information will be sent to the independent statistician for final analyses based on the prespecified statistical plan.

We defined 'failed OFA' as that haemodynamics preclude continued dexmedetomidine administration (severe bradycardia despite the use of atropine). In this situation, the dexmedetomidine infusion will be discontinued, and the patients will receive treatment at the clinician discretion. Sufentanil may have to be administered to these patients for the completion of anaesthesia and surgery. Serious adverse events (such as persistent haemodynamic instability or asystole) associated with the study medications or not should be immediately reported to the principal investigator (KP). In such situations, the perioperative care team should provide relevant treatment to ensure patient safety. Such events should also be reported to the DMC within 24 hours. The DMC will discuss and make recommendations on whether the study interventions should be modified and whether the study should be stopped.

### Sample size calculation

A recent study suggested that 41.7% of patients who received VATS and opioid-based anaesthesia experienced PONV and OFA reduced the incidence of PONV by ~90% (ie, from 41.7% to 4.3%).<sup>19</sup> However, a previous study showed that the use of OFA reduced the risk of PONV by ~45% (ie, from 37.3% to 20%) in bariatric surgery.<sup>9</sup> For power analysis in this study, we hypothesise that the incidence of PONV is 40% in the opioid-based control group. Based on the assumption of an average PONV reduction by 60%, we expect that our balanced OFA strategy would reduce the PONV incidence to 16%. To detect such a between-group difference in PONV at two-sided  $\alpha=0.05$  and power=80%, 53 patients in each group are required. Considering potential dropouts, we plan to enrol a total of 120 patients, with 60 in each group. The sample size calculation is performed using the PASS software (V.11.0.7, NCSS, Kaysville, Utah, USA).

### Statistical analysis

Continuous data will be checked for normal distribution with the Shapiro-Wilk test. Means (SDs) will be used for normally distributed data, and medians (IQRs) for data that are not normally distributed. Continuous data will be analysed using the independent t-test, Mann-Whitney rank-sum test or repeated measures analysis of variance, as appropriate. Categorical data will be presented as numbers (percentages) and analysed using the  $\chi^2$  test or Fisher's exact test. The between-group differences for the primary, secondary and safety outcomes will be analysed using mean difference or OR with 95% CIs. The primary outcome of PONV incidence will be further analysed in the subgroups of sex, smoking status and PONV risk scores. Multiple testing corrections for the secondary outcomes are not planned, so these outcomes should be considered exploratory.

All study outcomes will be analysed in the modified intention-to-treat population, including all patients who undergo randomisation with relevant data available. Patients will be included in the analysis according to their

original allocation. No interim analysis will be planned. Missing data will not be imputed. Statistical analyses will be conducted with the use of SPSS software (V.19.0; IBM SPSS). A two-sided p value of <0.05 indicates a statistically significant difference.

### Patient and public involvement

Patients and public will not be involved in the design, recruitment, conduct or report of the study. The study results will be disseminated to the participants via email.

### Ethics and dissemination

This study was approved by the Ethics Committee of the First Affiliated Hospital of Soochow University (2022-042) on 28 April 2022. The protocol was registered at the Chinese Clinical Trial Registry (ChiCTR2200059710) on 9 May 2022. All patients will provide written informed consent (online supplemental file 2), and the implementation of this study will conform to the Declaration of Helsinki. The results of this study will be published in a peer-reviewed journal.

### DISCUSSION

In this randomised controlled trial, we will enrol a total of 120 adult patients who undergo VATS lung resection to evaluate the effects of balanced OFA versus balanced opioid-based anaesthesia on PONV and postoperative pain outcomes. In addition, we will compare the two anaesthesia regimens in terms of length of PACU stay, length of postoperative hospital stay, perioperative safety outcomes, and 30-day and 90-day post-surgical pain and mortality. This study will be implemented in accordance with the Consolidated Standards of Reporting Trials guidelines.<sup>20</sup>

From the existing literature, OFA has been used for patients undergoing several of types surgery. Ziemann-Gimmel and colleagues suggested that opioid-free total intravenous anaesthesia was associated with reduced risk of PONV for patients undergoing bariatric surgery.<sup>9</sup> Bakan and colleagues reported that opioid-free propofol anaesthesia in laparoscopic cholecystectomy reduced postoperative fentanyl consumption, pain scores and need for ondansetron administration.<sup>10</sup> However, Massoth and colleagues showed that their balanced OFA strategy did not decrease PONV, postoperative pain or morphine requirement after gynaecological laparoscopy.<sup>11</sup> Boleil and colleagues showed that the balanced OFA led to an increased incidence of hypoxaemia, serious bradycardia, delayed extubation and prolonged PACU stay.<sup>12</sup> Hence, the effects of OFA in different surgical setting are inconsistent.

In a recent study, we reported the characteristics (opioid usage, PONV, pain scores, PACU stay, intensive care unit (ICU) admission and hospital stay) for VATS lung resection at our institution.<sup>21</sup> The results showed that: (1) the mean intraoperative sufentanil consumption was 0.74  $\mu\text{g}/\text{kg}$ ; (2) the incidence of PONV during postoperative

0–48 hours was 26.7%; (3) the mean pain scores were 2.2 at PACU discharge, 3.0 at postoperative 24 hours and 1.0 at postoperative 48 hours; (4) the mean length of PACU stay was 35 min; (5) no patient needed ICU admission; and (6) the mean length of postoperative hospital stay was 5 days. The observed PONV incidence in the previous study is lower than that of opioid-based control group (40%) in our power analysis, possibly because of the small number of patients (n=30). For postoperative pain control in that study, using tramadol on patients' request or when pain scores  $\geq 4$  provided adequate analgesia after surgery, and patient-controlled opioids were not used. In the present study, all patients will receive multimodal analgesia (wound infiltration with ropivacaine at the end of surgery, intraoperative flurbiprofen axetil and postoperative PCA with sufentanil). Wound infiltration is a safe and simple technique that is widely used for pain management in thoracic surgery.<sup>22–24</sup> Yang and colleagues also suggested that wound infiltration was not inferior to PCA with fentanyl in VATS lung resection.<sup>25</sup> Actually, the PCA used in our study is to provide rescue analgesia, with low background infusion rate and patient-controlled additional dose.

Two recent studies have investigated the use of OFA in VATS procedures. A retrospective study reported that OFA with dexmedetomidine, ketamine, lidocaine, and sevoflurane was safe and associated with reduced postoperative pain and morphine consumption.<sup>26</sup> A randomised study suggested that analgesia-antinociception offered by OFA with dexmedetomidine and sevoflurane was as effective as opioid-based anaesthesia with remifentanyl and sevoflurane.<sup>19</sup> However, the effects of OFA on postoperative pain and PONV for patients undergoing VATS are still unclear. Our balanced OFA regimen includes dexmedetomidine (0.6  $\mu\text{g}/\text{kg}$  over 10 min), esketamine (0.3 mg/kg) and propofol (1.5–2.0 mg/kg) for anaesthesia induction, followed by dexmedetomidine (0.2–1.0  $\mu\text{g}/\text{kg}/\text{hour}$ ), esketamine (0.1 mg/kg boluses), and sevoflurane for anaesthesia maintenance and intraoperative analgesia. As far as we know, this is the first randomised controlled trial powered to assess the effects of OFA on PONV after VATS lung resection.

This study has some limitations. First, the balanced OFA regimen is not definitive, and the optimal way to administer OFA in VATS lung procedures needs further investigation. Second, the sample size calculation is based on the incidence of PONV. The pain outcomes and other secondary outcomes should be interpreted as exploratory. Third, the anaesthesiologist cannot be blinded due to the differences between techniques. Nonetheless, they will not participate in other parts of the study, and the primary outcome of PONV is reported by patients themselves. Fourth, we do not use PONV severity scoring in this study. We will assess nausea, vomiting and need for antiemetic therapy separately as secondary outcomes. Last, as this is a single-centre trial, further studies evaluating the OFA regimen will be warranted to corroborate our findings.

In summary, this randomised controlled trial will determine the effects of balanced OFA on PONV, postoperative pain and postoperative sufentanil consumption after VATS lung resection. The results of this study will offer a new insight into improving anaesthetic care for patients undergoing VATS lung procedures.

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STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	Item No	Description	Addressed on page number
<b>Administrative information</b>			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	4
Protocol version	3	Date and version identifier	4
Funding	4	Sources and types of financial, material, and other support	14
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	14
	5b	Name and contact information for the trial sponsor	14
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	14
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	14
<b>Introduction</b>			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4
	6b	Explanation for choice of comparators	4
Objectives	7	Specific objectives or hypotheses	4
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5

**Methods: Participants, interventions, and outcomes**

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5-6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	6
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	6
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	6
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Table 1
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	10-11
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	10-11

**Methods: Assignment of interventions (for controlled trials)**

## Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	6
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	6
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	6
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	6

**Methods: Data collection, management, and analysis**

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	10
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	10
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	10
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	11
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	11
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	11

**Methods: Monitoring**

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	10
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	10
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	10
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	10

**Ethics and dissemination**

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	12
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	NA
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	12
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	10
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	15

Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	14
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	14
	31b	Authorship eligibility guidelines and any intended use of professional writers	NA
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
<b>Appendices</b>			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Online supplemental file 2
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

\*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](#)" license.

## Informed Consent

### Informed Page

**Name of Project:** Effect of balanced opioid-free anaesthesia on postoperative nausea and vomiting after video-assisted thoracoscopic lung resection

**Source of project:** The Science and Technology Development Plan Clinical Trial Project (SLT201909) and Jiangsu Provincial Medical Youth Talents Program (QNRC2016741).

**Project research organization:** Department of Anaesthesiology, First Affiliated Hospital of Soochow University, Suzhou, Jiangsu, China; Institute of Anaesthesiology, Soochow University, Suzhou, Jiangsu, China.

**Research leader:** Ke Peng

Dear Mr/Mrs,

You will be invited to participate in a clinical study. The following item describes the research background, purpose, research methods, benefits, possible discomfort, inconvenience, your rights, and your interests in the course of this study. Please read them carefully before attending the clinical study. This informed consent may help you decide whether to participate in this clinical study or not. You can ask questions to ensure you fully understand the content. If you agree to participate in the clinical study, please sign it on the signature page of the informed consent form.

## Research introduction

### I. Research background

Postoperative nausea and vomiting (PONV) is one of the most common adverse reactions after general anesthesia and surgery. Although various antiemetic drugs have been continuously developed, the incidence can be as high as 60-80% in surgical patients. The main risk factors for PONV include opioid use, women, non-smoking and previous motion sickness or history of PONV. Opioids have been widely used in clinical pain management, but its adverse reactions include nausea and vomiting, respiratory

depression, hyperalgesia, and impaired gastrointestinal motility. In recent years, the new concept of opioid anesthesia has emerged. In this study, we aim to evaluate the effects of OFA on PONV and postoperative pain in patients undergoing thoracoscopic pulmonary surgery.

## **II. Study name and purposes**

The name of this study is: Balanced opioid-free anaesthesia for patients undergoing video-assisted thoracoscopic lung resection: protocol for a randomised controlled trial. The primary outcome of this trial is the incidence of PONV within 48 hours after surgery.

## **III. Research methods and content**

By using the randomization method, we will assign you to one of the opioid-based or opioid-free groups. The two groups adopt different anesthesia induction and maintenance methods, and we will evaluate and analyze the medical information data that you have generated during your routine clinical anesthesia and postoperative recovery process. We will follow you up and ask you about the postoperative nausea, vomiting, pain and other related questions within 48h after the surgery.

The researcher began to arrange for the relevant examination and research operations. These examination and study operations will help to determine if you are fit to participate in this study. This stage is the "pre-study phase". If the investigator determines that you have not met the enrollment criteria, you will not be allowed to participate in the study. The investigator will advise you to follow the routine anesthesia protocol. After you understand the whole study and have had your questions satisfactorily answered, you will need to sign this informed consent form if you wish to participate in this study.

## **IV. Research process and time limit**

The entire study is expected to be completed within 1 year, and the total number of planned enrolled subjects is 120 (60 of each group). The study process consists of the screening period and the follow-up period. You will complete this study at approximately 90 days after surgery, without any other ancillary examinations.

## **V. Possible benefits of participating in the research**

Your participation in this study may help you to reduce the occurrence and severity of postoperative nausea and vomiting, and you will be carefully evaluated, monitored, and treated. At the same time, we hope to learn more about the impact of OFA on postoperative pain management through the information obtained from the institute. Based on these, we could accumulate experience for anesthesia management of future surgical patients and provide new ways and ideas for improving PONV.

#### **VI. Possible risks and discomfort of participating in the study**

You will receive general anesthesia in this study. Although general anesthesia has a good safety profile, the following risks may still occur perioperatively: (1) respiratory depression, respiratory tract obstruction, aspiration, asphyxia or aspiration pneumonia, and respiratory failure; (2) arrhythmia, hypotension, hypertension, and heart failure; (3) tooth loss, hoarseness, laryngeal edema, postoperative pain, nausea, vomiting, agitation, delayed awakening or intraoperative awareness; (4) high sensitivity or allergy, infusion and blood transfusion reactions; (5) electrolyte and acid-base balance disorder, hemorrhagic shock; (6) central and peripheral nerve injury, postoperative headache, and pulmonary complications. The safety of the anesthesia process is monitored by the attending anesthesiologist. Anesthesiologists are fully responsible for the detection and treatment of patients during the perioperative period according to the rules and regulations, operation routine and diagnosis and treatment norms. Before anesthesia, we will explain to the patients and their family members about the possible problems perioperatively. We will prepare and observe carefully and deal with any problem in time. In case of a life-threatening situation, we will ensure full rescue, and ask the patient and his family members to understand and support. The above content is detailed in the Informed Consent in the medical record, and will be signed by the patient or the authorized client.

The esketamine and other anesthetic drugs in this study are routinely used in clinical practice, so they will not increase the risks beyond the routine treatment. The anesthetics and other drugs (esketamine, sufentanil, propofol, cisatracurium, dexamethasone, sevoflurane) may induce adverse reactions, for which the treatment measures are as follows: (1) adverse effects of esketamine include dizziness, drowsiness,

gastrointestinal discomfort, increased blood pressure, increased heart rate and other adverse reactions. Benzodiazepines can effectively reduce the relevant discomfort symptoms; (2) adverse effects of sufentanil include respiratory depression, apnea, hypotension, bradycardia, nausea and vomiting. Supplementary oxygen administration, maintaining hemodynamic stability, antiemetic and other symptomatic treatment can reduce these adverse effects; (3) adverse effects of propofol include hypotension, injection pain, respiratory depression. Supplementary oxygen administration and intravenous lidocaine can reduce related adverse reactions of propofol; (4) adverse reactions of cisatracurium include delayed muscle strength recovery, rash and other adverse reactions. The use of antagonist of muscle relaxants can improve the recovery of muscle strength in patients; (5) adverse effects of dexamethasone include elevated blood glucose, which can be managed with glucose monitoring and insulin treatment if necessary.

For the common adverse effects that may occur during anesthesia, treatments are as follows: hypotension (SBP <90 mmHg or MAP reduction exceeds 30% above base value), intravenous ephedrine 6mg; Severe bradycardia (HR <45 bpm), intravenous atropine 0.3mg; Hypertension (systolic blood pressure >140mmHg or MAP increased by 30% above the base value) and tachycardia (HR> 100 bpm), uradil 5mg or esmolol 20mg was injected based on the depth of anesthesia and adequate analgesia; Hypoxemia (SpO<sub>2</sub> <90%), mask compression to assist in breathing, blood gas analysis was performed and symptomatic treatment was performed. PONV rescue treatment plan: if the patient occurs postoperative nausea and vomiting, ondansetron, haloperidol, metoclopramide and other treatments will be given according to the situation. Postoperative pain relief treatment plan: if the patient request or VAS score is greater than 3 or equal to 4, flurbiprofen axetil 50mg intravenous infusion, which can be repeated within 24 hours if necessary. If you have any discomfort, or new changes in your illness during the study, whether drug-related or not, timely notify your doctor, he / she will make a judgment and medical treatment, and will do anything possible to prevent and treat the risks and discomfort due to this study.

In addition, if someone other than the researcher has obtained your relevant health

information, it may cause employment, insurance, or trouble for your family. To reduce these risks, we will keep your personal information confidential under relevant regulations. In case of serious adverse reactions related to the study, we will immediately take the corresponding treatment measures, inform the ethics committee, and provide economic compensation in accordance with Chinese laws and regulations.

#### **VII. Treatment and financial compensation for study-related injuries**

If the participant suffers any injury related to the study and is determined by the authority stipulated by the national laws and regulations, the funding and institution will cover the relevant treatment expenses and the corresponding economic compensation according to the relevant laws and regulations of China.

#### **VIII. Routine diagnosis and treatment plan outside of this study**

In addition to participating in this study, you can take a routine opioid anesthesia induction and maintenance management protocol.

#### **IX. Rights of the subjects**

This study will not cause additional harm to your physical and psychologic status or social relationships, and will not affect the diagnosis and treatment of your disease. The whole study process is subject to the supervision of the ethics committee of our hospital. You can consult the study doctor with any questions during the study. Your participation in the trial is entirely voluntary, and you can withdraw informed consent at any time. Your personal data and observation records are confidential for this study only. During the trial, you can contact the study physician and research team members during the trial or consultation.

#### **X. Confidentiality of clinical research data**

The investigator is responsible for following the applicable data protection regulations to handle your research data. However, the information is accessible to the ethics committee and higher administrative departments. The results may be published in medical journals or conferences, but your identity will not be disclosed.

After signing this informed consent, you will give your consent to the research doctor and the research center staff to collect your health information data. Your authorization for us to use your health information remains valid until the study ends

and until the results are available. However, you can always withdraw your informed consent from the responsible physician through the study.

#### **XI. Collection and management of biological samples involving people**

The investigator declare that this study does not involve the collection and management of biological samples from the subjects.

#### **XII. Contact information**

All members of the research group will answer all of your questions before you sign this consent form. If you still have questions, suggestions, or comments after signing the consent form, you can communicate with the investigator. You can keep information about and progress of this study.

**Researchers and contact information:** Ke Peng, 15962155989, pengke0422@163.com

**Ethics Committee contact person and contact information:** Shuangjie Wu, 0512-67972743

#### **XIII. Statement and Signing**

Subject statement: I have read this informed consent form carefully; I have the opportunity to ask questions and all questions have been answered. I understand that participation in this study is voluntary, so I can refuse participating in this study, or withdraw from the study at any time without discrimination or retaliation, and my medical treatment and interests will not be affected.

If I need other treatment, have any other reasonable reason, or fail to comply with the study plan, the study doctor may terminate my continued participation in this clinical study.

I voluntarily agree to participate in this clinical study and I will receive a signed copy of the "informed consent form".

**Subject Name (regular script)** \_\_\_\_\_

**Subject Signature:** \_\_\_\_\_ **Mobile phone number:** \_\_\_\_\_

**Date:** \_\_\_\_\_

**Name of legal agent (regular script)** \_\_\_\_\_

**Signature of the legal agent:** \_\_\_\_\_ **Mobile phone number:** \_\_\_\_\_

**Relationship with the subjects:** \_\_\_\_\_

**Date:** \_\_\_\_\_

Reasons why the subjects could not sign the informed consent form: \_\_\_\_\_

The Investigator has stated that I have accurately informed the subject of the informed consent form and answered the questions, and the subject has volunteered to participate in this clinical study.

**Name of investigator** \_\_\_\_\_ **signature:** \_\_\_\_\_

**Mobile phone number:** \_\_\_\_\_

**Date** \_\_\_\_\_