


# BMJ Open Comparison of the effects of remimazolam tosylate and propofol on postoperative delirium among older adults undergoing major non-cardiac surgery: protocol for a randomised controlled trial

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## ABSTRACT

**Introduction** Postoperative delirium (POD) is a common cognitive disturbance in elderly individuals that is characterised by acute and fluctuating impairments in attention and awareness. Remimazolam tosylate is a novel, ultrashort-acting benzodiazepine, and there is limited evidence of its correlation with the incidence of early POD. The aim of this study is to evaluate the incidence of POD after anaesthesia induction and maintenance with remimazolam tosylate or propofol in elderly patients undergoing major non-cardiac surgery.

**Methods and analysis** This is a single-centre, randomised controlled trial. 636 elderly patients undergoing major non-cardiac surgery will be enrolled and randomised at a 1:1 ratio to receive total intravenous anaesthesia with either remimazolam tosylate or propofol. The primary outcome is the incidence of POD within 5 days after surgery. Delirium will be assessed twice daily by the 3 min Diagnostic Interview for the Confusion Assessment Method or the Confusion Assessment Method for the intensive care unit (ICU) for ICU patients. Secondary outcomes are the onset and duration of delirium, cognitive function at discharge and within 1-year postoperatively, postoperative analgesia within 5 days, chronic pain at 3 months, quality of recovery and postoperative inflammatory biomarker levels.

**Ethics and dissemination** The study was approved by the institutional ethics committee of the National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences (approval No. 22/520–3722). Written informed consent will be obtained from each patient before enrolment. The results of this trial will be presented at scientific conferences and in peer-reviewed scientific journals.

**Trial registration number** ChiCTR2300067368.

## INTRODUCTION

Postoperative delirium (POD), characterised by an acute change in mental status, commonly occurs after major surgery.<sup>1</sup>

## STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ A randomised controlled trial design will be used in this study to assess the incidence of postoperative delirium (POD) in elderly patients undergoing major non-cardiac surgery.
- ⇒ The study will include a longer-term follow-up and assess multiple dimensions of postoperative cognition, quality of recovery and inflammation levels.
- ⇒ Against the background of a high incidence of malignancies worldwide, our study will reflect the POD incidence of a homogenous population with tumours, except for brain tumours.
- ⇒ Although investigators cannot be blinded, the anaesthesia process and intraoperative data may be affected, a large sample size and strict randomisation may also minimise the confounding effect.

Although the incidence of POD in patients undergoing general surgery is 2–3%,<sup>2</sup> it increases with age. Previous studies have shown that the incidence of POD in elderly patients is between 5.7% and 71%,<sup>3–5</sup> often leading to longer hospitalisations, higher costs, worse functional recovery and even higher mortality.<sup>6,7</sup>

Although the incidence of POD is closely associated with the duration of anaesthesia, the relationship between POD and general anaesthetic drugs remains inconclusive. Midazolam and propofol are most commonly used for sedating patients. Propofol, which is commonly used in total intravenous anaesthesia, has the advantages of a rapid effect, no muscle twitching during induction, no adrenocortical inhibition and rapid recovery.<sup>8</sup> However, the disadvantages of propofol include potential respiratory depression, hypotension, injection pain and

hypertriglyceridaemia.<sup>9–11</sup> Additionally, the interaction between propofol and muscarinic acetylcholine receptors may be related to postoperative cognitive impairment.<sup>12</sup> Our previous meta-analysis study involving 1404 elderly patients with lung cancer revealed that propofol had a more significant adverse effect on cognitive function than sevoflurane.<sup>13</sup> Therefore, the identification of alternative sedatives in general anaesthesia has become an urgent priority.

Remimazolam is a novel, water-soluble, ultrashort-acting benzodiazepine that inhibits the central nervous system by acting on  $\gamma$ -aminobutyric acid receptors, thereby exerting sedative and amnestic effects.<sup>14</sup> It has the characteristics of high clearance, a small distribution volume, a short half-life, a rapid onset of action and inactivation with a terminal half-life of 0.75 hours.<sup>15</sup> Unlike propofol, remimazolam is metabolised by tissue esterases and eliminated by first-order pharmacokinetics.<sup>15</sup> Even high-dose bolus injections, prolonged infusion and administration in subjects with hepatic or renal impairment are unlikely to result in accumulation and extended effects.<sup>16,17</sup> Moreover, the sedative effect of remimazolam can be rapidly reversed by flumazenil, which increases the controllability.<sup>18</sup> A previous study on the use of remimazolam in general anaesthesia, based on a population pharmacokinetic (popPK) analysis of plasma concentration-time data from 11 Phase 1–3 clinical trials, as well as a population pharmacokinetic-pharmacodynamic (popPK-PD) analysis of concentration-bispectral index (BIS) data from eight trials, revealed that 6 mg/kg/hours of remimazolam until loss of consciousness followed by 1 mg/kg/hours during the period of general anaesthesia and 0.25 mg/kg/hours for postoperative sedation for up to 24 hours is safe and optimal, regardless of subjects' American Society of Anesthesiologists (ASA) class or sensitivity.<sup>19</sup> Moreover, available evidence suggests that the long-term use of oral benzodiazepines is associated with cognitive decline,<sup>20</sup> whereas single intraoperative doses do not increase the incidence of POD.<sup>21</sup> Although the rapid elimination of remimazolam might theoretically prevent POD,<sup>22</sup> the use of continuous intravenous infusion in total intravenous anaesthesia remains uncertain.

Remimazolam tosylate was approved for general anaesthesia in adult patients in China on 9 November 2021. Existing studies have adequately assessed its safety and efficacy,<sup>23–25</sup> while evidence of its effect on POD is limited. Accordingly, we designed a randomised, controlled trial to evaluate whether remimazolam tosylate or propofol can reduce the incidence of POD in older patients undergoing major non-cardiac surgery.

## METHODS AND ANALYSIS

### Objective

The primary objective of this study is to compare the incidence of POD in elderly patients undergoing major non-cardiac surgery who receive remimazolam tosylate with that in those who receive propofol. The secondary

objectives of the study are to evaluate the onset and duration of delirium, cognitive function within 1-year postoperatively, quality of recovery, acute and chronic postoperative pain and postoperative inflammatory biomarker levels.

### Study design

This is a single-centre, randomised, controlled study (figure 1). Participants will be recruited from the Cancer Hospital of the Chinese Academy of Medical Sciences, which is a tertiary academic hospital in China. The study was approved by the institutional ethics committee of the National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences (approval No. 22/520–3722) and has been registered in the Clinical Trial Registry. Written informed consent will be obtained from each patient before enrolment (online supplemental appendix). Eligible patients will be enrolled and randomly assigned to either of the two study groups. The protocol is reported according to the Standard Protocol Items: Recommendations for Interventional Trials reporting guidelines (figure 2).<sup>26</sup>

### Participants

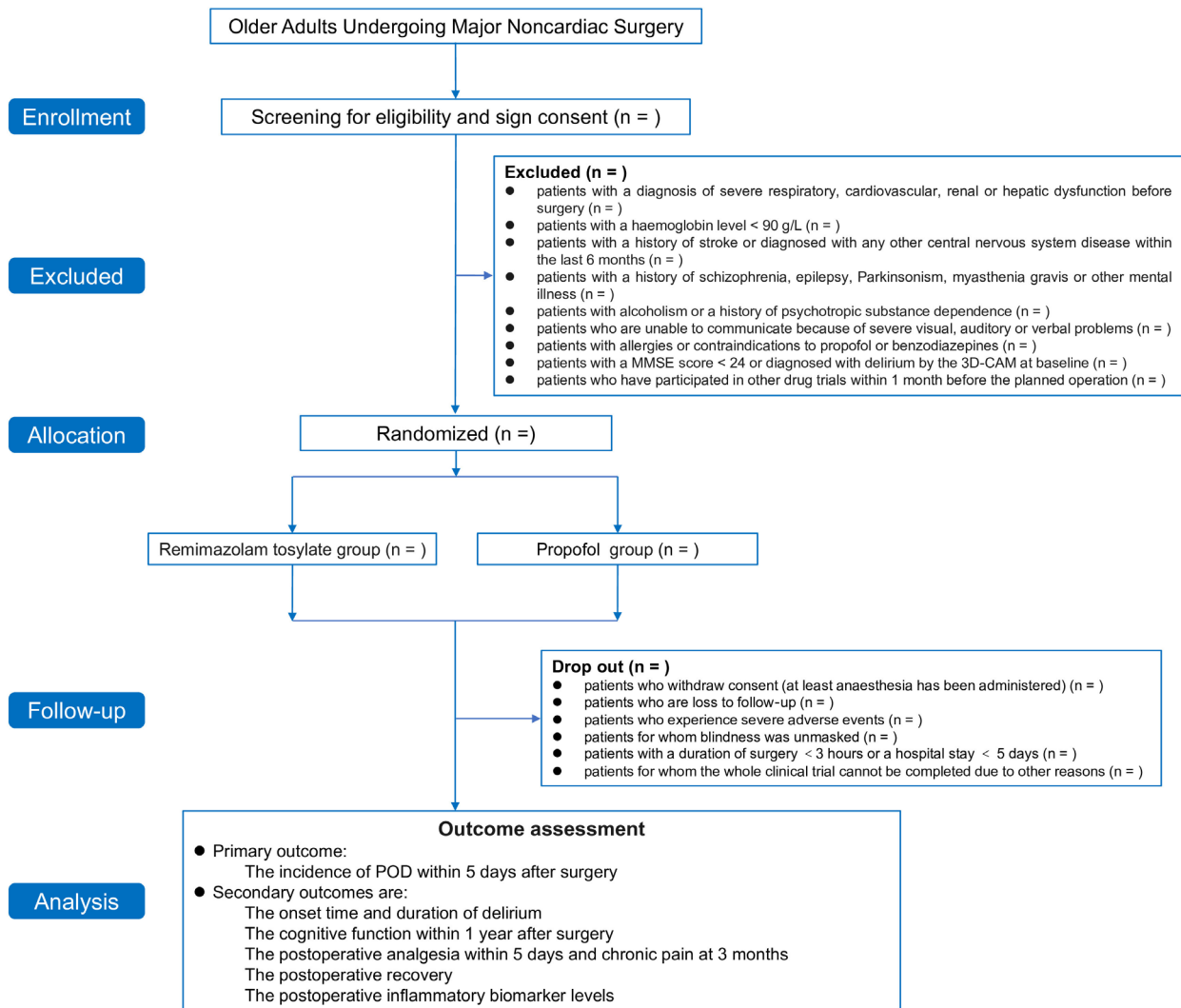
We will recruit 636 elderly patients undergoing major non-cardiac surgery according to the inclusion and exclusion criteria. We plan to enrol the first patient on 1 March 2023, and finish recruiting on 28 February 2025.

### Inclusion criteria

The inclusion criteria are as follows: (1) male or female patients between 65 and 90 years of age; (2) patients with an ASA physical status score  $\leq 3$ ; (3) patients scheduled to undergo major non-cardiac surgery with an expected duration of at least 3 hours and an anticipated hospital stay of at least 5 days; and (4) patients with a body mass index (BMI) between 18 and 27.9 kg/m<sup>2</sup>.

### Exclusion criteria

The exclusion criteria are as follows: (1) patients with a diagnosis of severe respiratory, cardiovascular, renal or hepatic dysfunction before surgery; (2) patients with a haemoglobin level  $<90$  g/L; (3) patients with a history of stroke or a diagnosis of any other central nervous system disease within the last 6 months; (4) patients with a history of schizophrenia, epilepsy, Parkinsonism, myasthenia gravis or other mental illness; (5) patients with alcoholism or a history of psychotropic substance dependence; (6) patients who are unable to communicate because of severe visual, auditory or verbal problems; (7) patients with allergies or contraindications to propofol or benzodiazepines; (8) patients with a Mini-Mental State Examination (MMSE) score  $<24$  or diagnosed with delirium by the Confusion Assessment Method (CAM) or the 3 min Diagnostic Interview for the Confusion Assessment Method (3D-CAM) at baseline; and (9) patients who have participated in other drug trials within 1 month before the planned operation.



**Figure 1** Study flowchart. ASA, American Society of Anesthesiologists; MMSE, Mini-Mental State Examination; POD, postoperative delirium; 3D-CAM: 3-min Diagnostic Interview for the Confusion Assessment Method.

### Dropout criteria

The dropout criteria are as follows: (1) patients who withdraw consent (at least after anaesthesia has been administered); (2) patients who are lost to follow-up; (3) patients who experience severe adverse events; (4) patients for whom blinding will be unsuccessful; (5) patients with a duration of surgery <3 hours or a hospital stay <5 days; and (6) patients for whom the whole clinical trial cannot be completed due to other reasons. The detailed reasons for cases of dropout will be recorded in the case report forms (CRFs).

### Rejection criteria

The rejection criteria are as follows: (1) patients who withdraw consent (before anaesthesia); (2) patients for whom surgery is delayed or cancelled; (3) patients whose case operation violates the protocol; and (4) patients with no study records or incomplete records due to other reasons. The detailed reasons for rejection will be recorded in the CRFs.

### Randomisation and masking

Randomisation at a 1:1 ratio will be achieved using SAS V.9.2 software (SAS Institute, USA), and participants will be enrolled and randomly assigned to either of the two study groups by an independent statistician. Treatment allocations will be sealed in opaque envelopes, and anaesthesiologists will not be informed of the anaesthesia strategy until the envelopes are opened before the induction of anaesthesia. Intraoperative data will be collected by unblinded anaesthesiologists. Investigators who are responsible for identifying potential participants according to the inclusion and exclusion criteria, performing follow-up in the postanaesthetic care units (PACUs) and the ward and collecting data on laboratory testing outcomes will all be blinded to randomisation throughout the study period. In case of an emergency (such as severe adverse events), unblinding will be permissible.

### Intraoperative monitoring and anaesthesia management

Standard intraoperative monitoring will include pulse oxygen saturation, non-invasive arterial blood pressure,



be given. If necessary, a repeated dose of 0.1 mg will be allowed.

#### Propofol group (P group)

Induction of general anaesthesia: propofol (2–3 mg/kg) will be intravenously injected; maintenance of general anaesthesia: propofol (4–10 mg/kg/hours) will be continuously infused.

#### Outcomes

The primary outcome will be the incidence of POD within 5 days after surgery. The secondary outcomes will be as follows: onset time and duration of delirium, cognitive function at discharge, cognitive function of 30-day survivors, cognitive function of 1-year survivors, postoperative analgesia within 5 days, postoperative chronic pain at 3 months, postoperative recovery (including quality of recovery, the occurrence of complications within 30 days and postoperative hospitalisation) and postoperative inflammatory biomarker levels.

#### Data collection and follow-up

Baseline data will include demographic data (age, sex, level of education and BMI), baseline mental assessment, preoperative diagnosis and tumour staging, smoking and alcohol history, diagnoses of comorbidities, preoperative medication use, surgical history and relevant laboratory test results.

Intraoperative data will include patients' vital signs, mechanical ventilation index, types and doses of anaesthetic drugs, durations of surgery and anaesthesia, types and volumes of fluids infused and blood transfusion status.

Patients will be followed-up twice daily (08:00 to 10:00 and 18:00 to 20:00) for five postoperative days and on the day of discharge (08:00 to 10:00). Patients will be interviewed via telephone at 30 days, 3 months, 6 months and 1 year after surgery. The collected data will include delirium and cognitive function evaluations, postoperative analgesia, Quality of Recovery-15 (QoR-15) scale scores and the occurrence of complications. If the patients are diagnosed with complications, the onset, duration and evidence will be documented.

#### Delirium assessment

The diagnosis and evaluation of POD will be overseen by a collaborating neuropsychologist (Dr Zhang Xiao of National Clinical Research Center for Mental Disorders (Peking University Sixth Hospital), Beijing, China). He will be responsible for training staff and arbitrating difficult cases. All researchers responsible for POD assessment will be required to receive training and obtain approval before commencing assessments. Once weekly, the cases that are difficult to evaluate will be referred to the collaborating neuropsychologist and discussed.

Delirium within 5 days after surgery will be assessed at baseline and twice daily by the 3D-CAM or the Confusion Assessment Method for the ICU (CAM-ICU) for ICU patients.<sup>29 30</sup> Because delirium often presents at night and

subsyndromal delirium increases the difficulty of diagnosis, abnormal situations (eg, inappropriate behaviour, confusion, hallucinations) will be recorded in detail by nurses or clinicians and reported to the collaborating neuropsychologist.

#### Cognitive function evaluation

Cognitive function will be evaluated at baseline, discharge, 30 days, 3 months, 6 months and 1 year postoperatively. The MMSE will be performed at baseline to identify undiagnosed cognitive impairment and at discharge to explore the association with POD (a difference between preoperative and postoperative MMSE scores  $\geq 2$ ).<sup>30 31</sup> The Telephone Interview for Cognitive Status-Modified (TICS-m) will be administered by telephone after discharge.<sup>32</sup> Total TICS-m scores range from 0 to 48, and higher scores indicate better cognitive function.

#### Assessments of postoperative analgesia

Postoperative pain will be evaluated by the Numerical Rating Scale (NRS), with scores ranging from 0 to 10 (0=no pain, 10=worst pain imaginable), at 1 hour, postoperative day 1, postoperative day 2, postoperative day 3, postoperative day 5 and 3 months postoperatively. The occurrence of three distinct types of pain will be recorded: superficial wound pain, pain at rest and pain during coughing. Forty-eight hours after surgery, the PCIA pump will be discontinued. The cumulative sufentanil consumption, rescue analgesia use and occurrence of nausea and vomiting will be recorded. During hospitalisation, if the NRS score is  $>3$ , flurbiprofen axetil (100 mg) will be administered intravenously for rescue analgesia; if the score is  $\geq 7$  for more than 24 hours, this situation will be defined as an adverse event, and all details will be recorded in the CRF.

#### Quality of recovery evaluation

Quality of recovery will be evaluated by the QoR-15 scale at postoperative day 1, postoperative day 3 and postoperative day 5.<sup>33</sup> It evaluates five dimensions: pain, physical comfort, physical independence, psychological support and emotional state.

#### Inflammatory biomarker assays

Postoperative inflammatory levels will be evaluated by the white blood cell (WBC) count and serum C-reactive protein (CRP) level. Peripheral venous blood samples will be taken at four time points: before the operation, and at postoperative day 1, postoperative day 3 and postoperative day 5. Blood samples will be analysed at the Cancer Hospital clinical laboratory using a Sysmex XN-9100 to detect the WBC count and a Beckman-AU5800 to detect the CRP level.

#### Adverse events

All adverse events observed by the investigators or reported spontaneously by the subjects will be recorded. Adverse events related to the study intervention and other factors may occur during the study, including (but

not limited to) hypertension, hypotension, tachycardia, bradycardia and respiratory depression. Serious adverse events refer to any unpredictable serious medical events such as persistent dysfunction, disability, life-threatening events or even death. The investigators will record any adverse events during the study and address them in accordance with the regulations. The recorded information will include the diagnosis, occurrence time, remission time, severity, relationship with the intervention, treatment and outcomes of adverse events. All serious adverse events will be reported to the Ethics Committee within 24 hours. Other adverse events will be reported in the final report. Patients with any adverse consequences directly caused by the research will be compensated in accordance with the law.

### Statistical analysis

#### Sample size

In a previous study, the incidence of POD after total intravenous anaesthesia with propofol in elderly patients was 33%,<sup>34</sup> and after usual anaesthetic care, it was 23%.<sup>35</sup> We assume that the incidence of POD in the remimazolam tosylate group will be 23%, which is consistent with usual anaesthetic care. With a significance level of 0.05 and a power of 80%, we estimated that 289 patients are needed in each group. Considering a loss-to-follow-up rate of approximately 10%, 318 patients will be needed in each group. The sample size was calculated with PASS V.16.0 software (StataCorp, College Station, Texas, USA).

#### Analyses

All statistical analyses will be performed with SPSS V.25.0 (IBM SPSS, USA) and the R software package by statisticians in the Office of Cancer Screening of the National Cancer Center. Since propofol and remimazolam tosylate will be administered according to the instructions and their safety has been confirmed by previous studies,<sup>16 25</sup> interim analysis is not planned.

#### Analysis sets

A full analysis set will include all eligible patients randomly assigned to either group with at least one follow-up evaluation. The per-protocol analysis set will include all patients meeting the eligibility criteria of the study with at least one follow-up evaluation after randomisation and with a treatment compliance rate of at least 80%. The safety set will involve all randomised patients with at least one safety assessment after randomisation.

#### Baseline data

The statistical description will be provided for baseline data, and the baseline balance will be assessed by the absolute standardised difference (ASD). Imbalance is defined as an ASD value greater than 0.2.

#### Outcome analysis

The primary outcome (the incidence of POD within 5 days after surgery) will be compared with the  $\chi^2$  test. The difference and the 95% CI of the difference will be

calculated. The Kaplan-Meier method combined with log-rank analysis will be used to determine the relationship between the incidence of POD and the time after major non-cardiac surgery.

For secondary outcomes, quantitative data will be compared using Student's t-test or the Mann-Whitney rank test. Categorical variables will be analysed with  $\chi^2$  or Fisher exact tests. Two-tailed p values < 0.05 will indicate statistical significance.

### Data management

Before recruitment, a password-protected electronic record will be established to store patient details. Their data will be encoded and identified by specific identification numbers that will be assigned. We will designate a trained investigator who is independent of the study to collect the research data and complete the case reports. The informed consent forms and the research data will be recorded in the corresponding electronic medical records, and the signed paper documents will be stored in a locked room in the hospital. Protected data sets will be backed up periodically (every 3 months) and synchronously audited by an independent data administrator. Only this administrator will be able to obtain the key for the identification codes during the study. The lead investigator will record and protect the data according to the guidelines at the end of the study. When recruitment and follow-up are completed, the data will be collected, entered and reviewed, all data queries will be completed and the data set will be locked. To help researchers understand and repeat the results, all data will be archived for 10 years after the study is completed. The details of the patients' identities will not be reported in any publication.

### Patient and public involvement

None.

### Ethics and dissemination

The study was approved by the institutional ethics committee of the National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences (approval No. 22/520-3722) and has been registered in the Clinical Trial Registry. This study will be conducted in accordance with the Helsinki declaration. Written informed consent will be obtained from each patient before enrolment (online supplemental appendix). The results of this trial will be presented at scientific conferences and in peer-reviewed scientific journals.

## DISCUSSION

Various risk factors related to POD have been reported previously. First, older age is the most common predisposing factor. A randomised study reported that the incidence of postoperative cognitive dysfunction in the first week after major non-cardiac surgery was 29% and 23% in patients aged over 70 years and in those aged between

60 and 69 years, respectively,<sup>36</sup> compared with an incidence of 2–3% for general morbidity.<sup>37</sup> Moreover, frailty, poor vision and hearing, multiple comorbidities, etc, in older patients have also been associated with an increased risk.<sup>38–40</sup> Second, surgery, anaesthesia, pain, etc, are also precipitating factors.<sup>40</sup> Major surgery is usually accompanied by a longer operative time, more intense postoperative pain and a greater risk of complications, all of which increase the risk of POD.<sup>41–43</sup> In a study of 1232 enrolled elderly patients undergoing major surgery, including cardiac surgery, with a median duration of anaesthesia of 264 min, the incidence of POD was 23.0–26.0%.<sup>35</sup> Among elderly patients, especially those who underwent cardiac surgery, the incidence was 10–28%.<sup>4</sup> However, in elderly patients ( $\geq 65$  years old) who underwent hip fracture surgery with a median duration of anaesthesia of 120 min, the incidence of POD was only 5.1–6.2%,<sup>3</sup> regardless of whether general or regional anaesthesia was adopted. These results suggest that elderly patients undergoing major surgery with a long anaesthesia duration are more prone to POD; hence, we included these susceptibility and predisposing factors in the inclusion criteria of our study, enrolling patients undergoing prolonged major surgical procedures for malignant tumours. In addition, the well-predefined risk factor for postoperative pain cannot be neglected for such a long duration of major surgery. First, most patients suffer from postoperative pain within 48 hours postoperatively; hence, PCIA is routinely used for acute pain relief in our cancer centre. Second, we will also perform an analgesia follow-up within 5 days. If the postoperative pain score is  $>3$ , flurbiprofen axetil (100 mg) or opioids, if necessary, will be administered intravenously for rescue analgesia, and the administration and analgesic effects will also be recorded. Third, as each patient has a different level of pain tolerance, if a patient suffers from continuous postoperative pain with an analgesia score  $\geq 7$  for more than 24 hours, the case will be defined as an adverse event and compared in the two groups by statistical analysis. Although postoperative pain cannot be completely avoided after major surgeries, which might produce confounding effects in our intervention, a large sample size and strict randomisation will help to balance and minimise this bias between the groups. Moreover, patients with brain tumours will be excluded to avoid the confounding effect of trauma interference on the incidence of POD in this study.

Delirium is a cognitive disturbance characterised by acute and fluctuating impairments in attention and awareness.<sup>37</sup> The CAM is the most widely used diagnostic algorithm and examines four features: an acute change in mental status with a fluctuating course (feature 1), inattention (feature 2), disorganised thinking (feature 3) and an altered level of consciousness (feature 4). Delirium will be diagnosed if the CAM indicates the presence of features 1 and 2 and either feature 3 or 4. The 3D-CAM and CAM-ICU are further optimisations of the CAM with wide acceptability worldwide because they are less time consuming and offer higher sensitivity and specificity.<sup>29</sup>

Hence, both algorithms have been chosen for diagnosing delirium in our study. Moreover, of all delirium patients, only 25% present with hyperactive delirium, and the remaining patients are diagnosed with hypoactive delirium.<sup>44</sup> For these relatively ‘quiet’ delirium patients, clinicians often face difficulties in diagnosis due to atypical symptoms. Hence, in this study, these cases will be diagnosed by collaborating neuropsychologists once weekly to increase diagnostic reliability. Moreover, a growing body of literature shows that POD is closely associated with long-term cognitive function.<sup>45–47</sup> A study including 103 participants who underwent valve replacement or coronary artery bypass grafting confirmed the relationship between cognitive impairment within 1 year after surgery and delirium.<sup>48</sup> In this study, cognitive changes will be followed-up through telephone questionnaires to assess the effect of remimazolam tosylate on long-term cognitive function.

The adoption of effective anaesthesia strategies to prevent POD is essential in older patients. Researchers hope to find a breakthrough in anaesthetic drugs to prevent POD. For commonly used inhaled and intravenous general anaesthetic drugs, some studies have shown that volatile anaesthetics have a greater impact on cognitive function than propofol,<sup>49</sup> some have also shown that cognitive function after sevoflurane anaesthesia was superior to that after propofol anaesthesia in patients with impaired cerebral oxygenation,<sup>50</sup> while others have suggested that there is no significant difference between the two anaesthesia strategies.<sup>51</sup> In addition, there is still some evidence revealing that low-dose dexmedetomidine significantly decreases the risk of POD in elderly patients admitted to the ICU after non-cardiac surgery,<sup>52</sup> while recent studies with large samples have shown that intraoperative dexmedetomidine does not prevent POD,<sup>53–55</sup> regardless of whether it is used for cardiac or non-cardiac surgery. Additionally, researchers hope to develop drugs that can reduce the risk of POD through anti-inflammation, analgesia and sympathetic arousal suppression mechanisms. Some studies have shown that acetaminophen combined with propofol or dexmedetomidine reduces the incidence of POD.<sup>4</sup>

This carefully designed, single-centre, randomised, controlled trial will be implemented in strict accordance with the protocol. However, there are some limitations in this study. First, pain and the administration of long-acting opioids may be associated with POD, inducing confounding effects in our results. Although there may be a discrepancy in the total opioid dosage between the two groups, a similar dose of hourly drug input volume for either group will be guaranteed. In addition, since the anaesthesiologists cannot be blinded to the interventions, this will not be a double-blinded clinical trial. In this study, the researchers will be blinded to the group allocation and/or the study hypothesis to reduce investigator bias. Moreover, the confounding effect may also be minimised by the large sample size and strict randomisation in this study.

Total intravenous anaesthesia with remimazolam tosylate causes minimal haemodynamic and respiratory depression in elderly patients. Compared with propofol, remimazolam tosylate may have an equivalent anaesthetic effect and a higher safety profile for elderly patients undergoing hip replacement, gastrointestinal endoscopy, bronchoscopy and general anaesthesia.<sup>56–58</sup> Moreover, previous literature has also proven remimazolam tosylate's availability as a general anaesthetic for continuous infusions during procedures longer than 2 hours.<sup>59</sup> However, research on the effect of remimazolam tosylate on the incidence of POD is very limited. Only one study showed that 0.1 mg/kg of remimazolam tosylate did not affect cognition recovery in elderly patients who underwent upper gastrointestinal endoscopy.<sup>60</sup> At present, another similar study enrolling cardiac surgery patients is in progress.<sup>61</sup> The subjects in this study will be a homogenous population with malignant tumours except for brain tumours. Unlike benign surgical approaches, lymph node dissection is the most challenging step during the entire process of removing tumours, leading to increased surgical trauma, stress and subsequent postoperative pain, prolonged anaesthesia duration and major surgical complications. Under the background of a high incidence of malignancies worldwide, our study will reflect the POD incidence of a homogenous population with tumours except for brain tumours in real-world practice. Additionally, this will be the first study with a large sample to compare remimazolam tosylate with propofol in terms of the incidence of POD among elderly patients undergoing major non-cardiac surgery.

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**Contributors** H-xL, TY and HZ helped to design this clinical trial. H-xL and B-IL helped with drafting the paper. XinZ and H-yL will be responsible for the acquisition of data. FW, BM and Y-IS will perform the statistical analysis. XiaoZ and XX will be responsible for conducting the postoperative cognitive survey. T-hW helped with the English language revision. All the authors contributed to the development of the trial. TY performed a critical revision of the manuscript. All the authors read and approved the final manuscript.

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