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# Evaluation of Remimazolam Tosilate Combined with Flumazenil versus Etomidate for Anesthesia in Elderly Patients Undergoing Prostate Biopsy: A Randomized Controlled Trial Protocol

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**Study protocol**

**Keywords:** Prostate biopsy, Recovery, ERAS, Elder, Remimazolam, Etomidate, Flumazenil

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**Additional Declarations:** No competing interests reported.

# Abstract

• **Background:**Prostate cancer is the most common malignancy among men globally, with a higher incidence in older males. The increasing aging population exacerbates the burden of this disease. Transperineal prostate biopsy under ultrasound guidance is considered the "gold standard" for diagnosis; however, patients often experience significant pain, adverse emotions, and severe stress reactions during the procedure, particularly elderly patients. An ideal anesthetic regimen, in line with the principles of ERAS, should be characterized by rapid onset, short duration, hemodynamic stability, minimal respiratory depression, and swift recovery. This study investigates the differences in anesthetic efficacy and recovery quality between remimazolam and etomidate in elderly patients undergoing prostate biopsies. Although etomidate is commonly used in elderly patients due to its hemodynamic stability, its metabolism is dependent on liver and kidney function, and it has multiple limitations including poor controllability, adrenal suppression, muscle twitching, injection pain, and prolonged recovery time. In contrast, remimazolam offers rapid onset, short half-life, minimal respiratory depression, low incidence of nausea and vomiting, and can be quickly reversed with flumazenil, potentially leading to more predictable recovery times and fewer adverse reactions.

• **Methods:** This study involved the administration of total intravenous anesthesia in elderly patients undergoing prostate biopsy, utilizing sufentanil for analgesia, followed by either etomidate or remimazolam for sedation. Flumazenil was administered at the end of the procedure to reverse the effects of remimazolam. The primary outcome was to compare the recovery time and quality of recovery in patients receiving remimazolam with those receiving etomidate.

• **Discussion:** This study aims to conduct a randomized controlled study to systematically evaluate the efficacy (anesthetic recovery and quality) and safety (haemodynamic/respiratory events and adverse reactions) of these etomidate and remimazolam-flumazenil in elderly patients undergoing transperineal prostate biopsy. thereby enhancing patient comfort and satisfaction during medical care.

• **Trial registration:** The registration number: Chinese Clinical Trial Registry (ChiCTR2400091993).Date of registration: 24 October 2024


# Structured summary {1b}

| Item | Description |
| --- | --- |
| Primary Registry and Trial Identifying Number {4} | Chinese Clinical Trial Registry (ChiCTR2400091993). |
| Secondary Identifying Numbers | None |
| Source(s) of Monetary or Material Support | This study was funded by Jiangsu Hengrui Pharmaceutical Co., Ltd. |
| Primary Sponsor and contact information {3b} | Sponsor:Jiangsu Hengrui Pharmaceutical Co., Ltd.<br>Grant recipient: Yaomin Zhu<br>Department of Anesthesiology, The First Affiliated<br>Hospital of Xi'an Jiaotong University, No.277, Yanta West Road, Yanta District, Xi'an, 710000,China<br>Email: yaomin_zhu@126.com |
| Role of sponsor and funder {3c} | The funder had no role in the analyses and<br>interpretation of the results or writing of the<br>manuscript. |
| Contact for Public Queries | Department of Anesthesiology, The First Affiliated Hospital of Xi'an Jiaotong University, 02985323250 |
| Contact for Scientific Queries | *Professor Yaomin Zhu, email: yaomin_zhu@126.com* |
| Public Title | A Study on Anesthesia Methods for Prostate Biopsy in Elderly Patients |
| Scientific title | Evaluation of Remimazolam Tosilate Combined with Flumazenil versus Etomidate for Anesthesia in Elderly Patients Undergoing Prostate Biopsy: A Randomized Controlled Trial Protocol |
| Countries of Recruitment | China |

| | |
|---|---|
| Health Condition(s) or Problem(s) Studied | this study aims to conduct a randomized controlled study to systematically evaluate the efficacy (anesthetic recovery and quality) and safety (haemodynamic/respiratory events and adverse reactions) of these etomidate and remimazolam-flumazenil in elderly patients undergoing transperineal prostate biopsy. thereby enhancing patient comfort and satisfaction during medical care. |
| Intervention(s) | • Induction:All patients will receive sufentanil 0.1 μg/kg intravenously 2 minutes before induction. The A group will receive remimazolam tosilate 0.2 mg/kg IV over 60 s; the B group will receive etomidate 0.3 mg/kg IV. Surgery will begin after loss of eyelash reflex, and all biopsies will be performed by the same surgeon.<br>• Maintenance:A group: remimazolam tosilate 0.4–1 mg/kg/h infusion;B group: etomidate 0.6–1.2 mg/kg/h infusion;BIS maintained between 40–60.Supplemental bolus of remimazolam (0.05 mg/kg) or etomidate (0.05 mg/kg) will be administered if anesthesia is inadequate (e.g. movement, sweating, lacrimation, hypertension, or tachycardia).Hypoxemia ($SpO_2$<93%) will be managed with jaw support or mask ventilation; if unresolved, LMA or intubation will be performed.Hypotension (MAP <55 mmHg) will be treated with norepinephrine 8 μg; bradycardia (HR <50 bpm) will be treated with atropine 0.5 mg.<br>• Recovery: At the end of the procedure, infusion will be stopped.A group: flumazenil 0.2 mg IV; if incomplete recovery within 60 s, an additional 0.1 mg every minute up to 0.5 mg total.B group: equal volume of saline. |
| Key Inclusion and Exclusion Criteria | 1. Inclusion criteria:<br>2. Scheduled for ultrasound-guided transperineal prostate biopsy.<br>3. Age ≥65 years.<br>4. BMI between 18 and 30 kg/m².<br>5. NYHA class I–II cardiac function.<br>6. ASA physical status I–III.<br>7. Patient and family understand the study, voluntarily participate, and sign written informed consent.<br>8. Exclusion criteria:<br>9. Allergy to remimazolam or etomidate.<br>10. Severe pulmonary disease or poor respiratory reserve (home oxygen therapy or non-invasive ventilation required, or exercise tolerance <4 METs).<br>11. Severe hepatic dysfunction (Child–Turcotte–Pugh >9).<br>12. Severe renal dysfunction (preoperative dialysis required).<br>13. Severe cardiac dysfunction (exercise tolerance <4 METs or LVEF <40%).<br>14. Severe psychiatric disease or cognitive impairment.<br>15. Participation in another clinical trial within 4 weeks before enrollment.<br>16. History of drug or alcohol abuse.<br>17. Withdrawal criteria:<br>18. Withdrawal of consent.<br>19. Severe adverse events during the trial (e.g., tracheal intubation required, or death).<br>20. Incomplete follow-up data preventing outcome assessment. |
| Study Type | This is a prospective, single-blind, randomized controlled superiority trial with a 1:1 allocation ratio between the experimental and control group. |

| | |
|---|---|
| Date of First Enrollment (planned) | The study was conducted using the latest version of the protocol and started in May 2025, with an expected duration of approximately 16 months, ending in September 2026. At the time of manuscript submission, patient recruitment had commenced, and the date of first enrollment was September 8, 2025. |
| Sample Size | 250 |
| Primary outcome(s) | Recovery time |
| Key Secondary outcome(s) | 1. Quality of Recovery: To evaluate the patients' Digit Symbol Substitution Test (DSST) scores at 30 and 60 minutes post-recovery, as well as the Post-anesthesia care unit (PACU) length of stay and patient satisfaction, to understand the overall effectiveness of the different anesthetic approaches.<br>2. Adverse Reactions: To monitor the incidence of adverse reactions during the perioperative period in both groups, including respiratory depression, hypotension, injection pain, re-sedation, emergence agitation, nausea and vomiting, and the usage of antiemetics (ondansetron), in order to compare the safety profiles of the two anesthetic regimens. |
| Ethics Review | The study protocol has been approved by the Ethics Committee of the First Affiliated Hospital of Xi'an Jiaotong University (approval number: XJTU1AF2024LSYY-368). |
| Individual Trial Participant Data sharing statement | Due to China's data protection laws and regulations, participant-level datasets cannot be publicly provided. If needed, please email the corresponding author to request the statistical code. |

**Protocol version {2}**

Version date: 1 May 2025

Version identifier: 1.2

# Introduction

**Background and rationale {9a}**

Prostate cancer is one of the most prevalent malignant tumors among men globally, with its incidence and mortality rates remaining alarmingly high. According to the "2022 Global Cancer Statistics," prostate cancer ranks as the second most common cancer and the fifth leading cause of cancer-related death in men, while in the Chinese male population, it ranks sixth and seventh, respectively[1]. With rapid socioeconomic development and an increasing aging population, the burden of prostate cancer in China continues to rise[2,3]. This malignant tumor predominantly affects elderly males, with the detection risk in individuals aged 65 and older being nearly 40 times higher than that in younger populations[4]. Transrectal ultrasound-guided transperineal prostate biopsy remains the gold standard for the diagnosis of prostate cancer[5]. The insertion of a transrectal ultrasound probe and perineal puncture during this

procedure, performed while the patient is awake, may result in severe pain, as well as adverse emotional responses such as anxiety and fear[6,7], significantly affecting patient comfort and compliance. Therefore, implementing appropriate analgesia and sedation is crucial to mitigate excessive stress responses, reduce the incidence of perioperative complications, and expedite postoperative recovery in patients undergoing prostate biopsy. The patient demographic is primarily elderly individuals, who often present with comorbid cardiovascular, cerebrovascular, or respiratory diseases, as well as declining liver and kidney function with age[8-10]. The pharmacokinetic and pharmacodynamic changes in this population lead to a reduced clearance rate and diminished tolerance to anesthetic agents[9]. When conducting day surgery for elderly patients, an ideal anesthesia regimen must meet several core requirements: rapid onset, short duration, maintenance of hemodynamic stability, low degree of respiratory suppression, and prompt and complete recovery. These characteristics are highly aligned with the principles of ERAS, which not only improve patient comfort and satisfaction but also optimize the efficiency of healthcare resource utilization[11,12]. Therefore, it is crucial to select an anesthesia plan that minimizes physiological disturbance, reduces adverse effects, and ensures optimal recovery quality.

Etomidate has long been used in this setting due to its haemodynamic stability, minimal respiratory depression, and rapid onset[13,14]. Studies have demonstrated that etomidate induction in elderly ambulatory patients reduces the requirement for vasoactive drugs to maintain haemodynamic stability[15]. However, etomidate lacks a specific antagonist, and adverse effects such as adrenal suppression, injection pain, myoclonus, and postoperative nausea and vomiting  limit its clinical application[16-18]. More importantly, controversy remains regarding whether etomidate prolongs recovery. Some studies have indicated that recovery times with etomidate may be longer than with propofol, and that increasing doses may progressively delay respiratory recovery, eye opening[19,20], and orientation, possibly due to GABA receptor desensitisation mechanisms[20].

Remimazolam tosilate, in contrast, is a novel ultra-short-acting intravenous benzodiazepine anesthetic that exerts sedative effects through GABA receptor activation[21,22]. It has rapid onset (1–3 minutes), a short elimination half-life (~0.75 hours), and is metabolised by tissue esterases in a non-organ-dependent manner, producing inactive metabolites[23-27]. These pharmacokinetic properties result in minimal accumulation even with continuous infusion and highly predictable recovery. The greatest advantage of remimazolam is its ability to be rapidly antagonised by flumazenil, enabling immediate termination of sedation, thus markedly improving controllability and safety[28].Recent studies suggest that compared with propofol or etomidate, regimens combining remimazolam with flumazenil significantly shorten awakening and cognitive recovery times, while maintaining more stable haemodynamic profiles. Moreover, adverse events such as injection pain, respiratory depression, and PONV are less frequent[29-32].

Nevertheless, potential risks of re-sedation after flumazenil reversal warrant attention[33]. The mechanism may be related to redistribution of flumazenil as a competitive antagonist, with increased risks in cases of high dosing or impaired clearance[34,35].

To date, despite the theoretical advantages of the remimazolam–flumazenil regimen, high-quality evidence directly comparing it with the commonly used regimen of etomidate in elderly patients undergoing transperineal prostate biopsy is lacking. This trial therefore aims to conduct a randomized controlled study to systematically evaluate the efficacy (anesthetic recovery and quality) and safety (haemodynamic/respiratory events and adverse reactions) of these two anesthetic regimens in this specific population. The findings are expected to provide an evidence-based reference for optimizing anesthesia strategies in elderly patients of day surgery.

**Explanation for the choice of comparator {9b}**

Etomidate is one of the commonly used sedative agents in intravenous anesthesia, functioning as a positive allosteric modulator of GABAA receptors to induce hypnosis [36]. Compared to other anesthetics, etomidate's hemodynamic stability is a notable advantage; at a dosage of 0.3 mg/kg for induction, it typically does not cause significant hypotension. This is due to etomidate's minimal suppression of sympathetic tone and preservation of autonomic reflexes, such as baroreflexes [37]. It has a rapid onset of action and a short elimination half-life when administered intravenously [13]. Given that elderly patients often present with multiple comorbidities and reduced cardiovascular reserve [10], the aforementioned properties of etomidate make it suitable for anesthesia in short procedures like prostate biopsies. However, etomidate is primarily cleared by the liver and kidneys [13], lacks a specific antagonist, has limited controllability, and may lead to adverse effects such as adrenal insufficiency, myoclonus, and nausea/vomiting [15-17], which could negatively impact postoperative recovery. Consequently, this study selects etomidate as a control drug to compare its effects with remimazolam tosilate in terms of anesthesia recovery time, recovery quality, and incidence of adverse reactions in elderly patients undergoing prostate biopsy.

**Objectives {10}**

This study aims to compare the anesthetic effects of toremifene sodium combined with flumazenil versus etomidate in elderly patients undergoing prostate biopsy. The specific objectives include:

1.Recovery Time: To compare the differences in awakening time between the two groups, assessing the impact of different anesthetic methods on the speed of recovery.

2. Quality of Recovery: To evaluate the patients' Digit Symbol Substitution Test (DSST) scores at 30 and 60 minutes post-recovery, as well as the Post-anesthesia care unit (PACU) length of stay and patient satisfaction, to understand the overall effectiveness of the different anesthetic approaches.

3. Adverse Reactions: To monitor the incidence of adverse reactions during the perioperative period in both groups, including respiratory depression, hypotension, injection pain, re-sedation, emergence agitation, nausea and vomiting, and the usage of antiemetics (ondansetron), in order to compare the safety profiles of the two anesthetic regimens.

Through these specific indicators, this study aims to provide essential evidence for improving the clinical experience and facilitating rapid postoperative recovery in elderly patients with prostate cancer.

# Methods: Patient and public involvement, and trial design

**Patient and public involvement {11}**

Patients or members of the public were not involved in the design, conduct, reporting, or dissemination plans of this research. The research questions, study outcomes, and methodology were determined by the investigators based on current clinical practice needs and evidence gaps. The study protocol, consent forms, and patient information sheets were reviewed and approved by the institutional ethics committee prior to implementation. The results will be disseminated to participants and the public through academic publications and presentations.

**Trial design {12}**

This is a prospective, single-blind, randomized controlled superiority trial with a 1:1 allocation ratio between the experimental and control group.The study will follow the CONSORT 2010 guidelines and SPIRIT recommendations for enrollment and assessments. The study flow is summarized in Figure 1.

**Methods: Participants, interventions and outcomes**

**Trial setting {13}**

The study is performed at the First Affiliated Hospital of Xi 'an Jiaotong University.

**Characteristics of the people who are needed for the trial**

| Characteristic | The people we would expect to see included |
|---|---|
| Age | Planned recruitment of participants aged ≥65 years. |
| Sex | Planned recruitment of Male. |
| Gender | Planned recruitment of man. |
| Race, ethnicity and ancestry | Planned recruitment of Asians. |
| Socioeconomic status | Not classified; socioeconomic status will not be a selection criteria for recruitment. |
| Geographic location | Expected recruitment in urban and rural areas of China. |
| Other characteristics relevant to the trial | • Smoking status: Current smokers, former smokers, and non-smokers will be recorded.<br>• Physical activity level: Participants will be categorized as sedentary, moderately active, or highly active.<br>• Presence of caregivers or family support postoperatively will be noted.<br>• Current medication use, specifically noting any anticoagulants or medications affecting liver or renal function. |

**Eligibility criteria for participants {14a}**

4. Inclusion criteria:

- Scheduled for ultrasound-guided transperineal prostate biopsy.
- Age ≥65 years.
- BMI between 18 and 30 kg/m².
- NYHA class I–II cardiac function.
- ASA physical status I–III.
- Patient and family understand the study, voluntarily participate, and sign written informed consent.

5. Exclusion criteria:

- Allergy to remimazolam or etomidate.

- Severe pulmonary disease or poor respiratory reserve (home oxygen therapy or non-invasive ventilation required, or exercise tolerance <4 METs).
- Severe hepatic dysfunction (Child–Turcotte–Pugh >9).
- Severe renal dysfunction (preoperative dialysis required).
- Severe cardiac dysfunction (exercise tolerance <4 METs or LVEF <40%).
- Severe psychiatric disease or cognitive impairment.
- Participation in another clinical trial within 4 weeks before enrollment.
- History of drug or alcohol abuse.

6. Withdrawal criteria:

- Withdrawal of consent.
- Severe adverse events during the trial (e.g., tracheal intubation required, or death).
- Incomplete follow-up data preventing outcome assessment.

**Eligibility criteria for sites and those delivering interventions {14b}**

1. Eligibility Criteria for Site:

This is a single-center study conducted at The First Affiliated Hospital of Xi'an Jiaotong University with expertise in urology and anesthesiology. And the center have the necessary infrastructure and equipment for performing ultrasound-guided transperineal prostate biopsies and administering anesthesia.

2. Eligibility Criteria for Individuals Delivering Interventions:

Urologists:

Must possess board certification or equivalent in urology.

A minimum of two years of experience in performing transperineal prostate biopsies.

Anesthesiologists:

Must be board-certified or eligible anesthesiologists with a minimum of three years of experience in administering anesthesia for urological procedures.

Must have current certifications in advanced cardiac life support (ACLS) or equivalent.

Anesthesia Nurses:

Must be registered nurses with a specialization in anesthesia.

A minimum of one year of clinical experience in operating room or procedural sedation contexts.

**Who will take informed consent? {32a}**

All participants will sign written informed consent prior to enrollment. Anesthesiologist A (not involved in the anesthesia) will explain the purpose, benefits, and risks of the clinical trial to patients meeting the inclusion criteria. Upon obtaining consent from the patients and their legally authorized representatives, the informed consent form will be signed. In cases where the patient is unable to provide consent, consent will be obtained from their legal representative in accordance with the laws of the People's Republic of China.

**Additional consent provisions for collection and use of participant data and biological specimens {32b}**

This study does not involve the collection of biological specimens. Accordingly, there are no additional consent provisions related to the use of biological samples. The consent obtained from participants will focus solely on the collection and use of clinical data related to the evaluation of anesthetic effects during ultrasound-guided transperineal prostate biopsies.

**Intervention and comparator**

**Intervention and comparator description {15a}**

Preoperative preparation:

Patients will be monitored with ECG, NIBP, $SpO_2$, and BIS. Baseline values will be recorded. Oxygen (4 L/min) via nasal cannula will be administered until full recovery. Anesthesiologist B is responsible for administering anesthesia and researching interventions.

Induction:

Before the surgery begins, both groups of patients will receive sufentanil 0.1 μg/kg. Two minutes later, the experimental group will receive remimazolam tosylate 0.2 mg/kg for anesthesia induction within 60 seconds, while the control group will receive etomidate 0.3 mg/kg for anesthesia induction.Surgery will begin after loss of eyelash reflex, and all biopsies will be performed by the same surgeon.

Maintenance:

A group: remimazolam tosilate 0.4–1 mg/kg/h infusion;

B group: etomidate 0.6–1.2 mg/kg/h infusion;

BIS maintained between 40–60.

Supplemental bolus of remimazolam (0.05 mg/kg) or etomidate (0.05 mg/kg) will be administered if anesthesia is inadequate (e.g. movement, sweating, lacrimation, hypertension, or tachycardia).

Hypoxemia ($SpO_2$<93%) will be managed with jaw support or mask ventilation; if unresolved, LMA or intubation will be performed.

Hypotension (MAP <55 mmHg) will be treated with norepinephrine 8 μg; bradycardia (HR <50 bpm) will be treated with atropine 0.5 mg.

Recovery: At the end of the procedure, infusion will be stopped.

A group: flumazenil 0.2 mg IV; if incomplete recovery within 60 s, an additional 0.1 mg every minute up to 0.5 mg total.

B group: equal volume of saline.

All patients will be transferred to PACU for at least 30 minutes. Aldrete scores will be recorded every 5 min; with joint assessment by anesthesiologist C and nurse anesthetist (not involved in the anesthesia). Patient are allowed to be discharged when the score is ≥9. Ondansetron 4 mg IV will be administered for severe PONV.

The intervention manual can be obtained by contacting the corresponding author by email.

**Criteria for discontinuing or modifying allocated intervention/comparator {15b}**

If Richmond Agitation-Sedation Scale (RASS) cannot be maintained between 0 and –2 within 3 min despite maximum infusion doses (remimazolam 1 mg/kg/h, etomidate 1.2 mg/kg/h), study drug will be discontinued and replaced by propofol infusion 4–12 mg/kg/h.Dosage will be recorded.

**Strategies to improve adherence to intervention/comparator {15c}**

1. Strategies to Improve Adherence to Intervention Protocols:

Although this study focuses on anesthetic agents, adherence to the intervention protocols will be ensured through several strategies. All anesthesiologists and clinical staff involved in the study will undergo training to understand the study objectives and the specific anesthetic protocols being implemented. A standardized anesthesia administration guideline will be followed to ensure uniformity in the anesthetic care provided to all participants.

2. Procedures for Monitoring Adherence:

To monitor adherence to the anesthetic protocol, detailed records of the anesthetic agents used, their dosages, and patient responses will be maintained for each procedure. Additionally, postoperative follow-up assessments will be conducted to evaluate the effectiveness and safety of the anesthesia, ensuring that any deviations from the protocol (e.g., dosage adjustments) are documented and addressed. These procedures will help confirm adherence to the study protocol and allow for the assessment of outcomes related to adherence.

**Concomitant care permitted or prohibited during the trial {15d}**

No additional sedatives or analgesics other than sufentanil and the study drug will be permitted.

**Ancillary and post-trial care {34}**

1. After evaluation by the anesthesiologist (Dr. C), who determines that the patient meets the criteria for discharge from the recovery room, the patient will be informed of the postoperative care instructions. Subsequently, the patient will be accompanied by the anesthesiologist and nursing staff to the day ward for specialized postoperative care.
2. In the event that an adverse reaction occurs during the perioperative period and is identified as a study-related harm, the sponsor will assume responsibility for medical expenses in accordance with relevant Chinese laws and regulations and will provide appropriate compensation. To safeguard patient rights, the sponsor has secured relevant insurance for this clinical trial. In cases where the insurance does not cover certain expenses, the sponsor will supplement those costs; however, damages arising from medical malpractice will be excluded from this compensation.

**Outcomes {16}**

1. Primary Endpoint: recovery time

1. Definition of Primary Endpoint: The primary endpoint of this study is defined as the interval from the cessation of drug administration and completion of the antagonist/placebo bolus to the time of the patient's first eye opening.
2. Evaluation of Primary Endpoint: After stopping the study drug infusion and completing the administration of the antagonist or physiological saline, anesthesiologist C will call the patient's name every 15 seconds, prompting the patient to open their eyes. Prior to the anesthesia, the patient will be instructed to open their eyes immediately upon hearing their name called.

2. Secondary Endpoints

The secondary endpoints focus primarily on the recovery from anesthesia and safety. Measurement indicators include:

1. The time to successful induction of anesthesia (the time from administration of toremifene sodium or etomidate to the disappearance of the corneal reflex).
2. PACU length of stay (the patient may leave the recovery room only when the modified Aldrete score is greater than 9).
3. DSST scores at 30 minutes and 60 minutes post-anesthesia to assess the quality of anesthetic recovery.
4. patient satisfaction：It will be evaluated using the Iowa State Anesthesia Satisfaction Scale (ISAS).
5. Safety-related indicators:

- Incidence of respiratory depression: The rate of patients with a respiratory rate of <8 breaths/min or oxygen saturation <93% will be recorded.
- Incidence of hypotension: Blood pressure will be measured every 3 minutes during the procedure, recording the incidence of mean arterial pressure (MAP) <65 mmHg or a reduction of >20% from baseline, along with the dosage of vasopressors (norepinephrine).
- Incidence of injection pain: The rate of patients reporting pain or exhibiting withdrawal movements in the arm will be recorded.
- Incidence of myoclonus after injection.
- Incidence of re-sedation in patients (defined as a reduction in RASS score of ≥1 point, assessed every 10 minutes during PACU; RASS will also be reassessed before leaving PACU and 2 hours after leaving PACU).
- Incidence of nausea and vomiting, along with the dosage of antiemetics (ondansetron).

**Harms {17}**

The anticipated harms associated with toremifene sodium remimazolam, an approved medication with established safety and efficacy, will be monitored throughout the study. The principal investigator will systematically record all adverse events, including:

- Severe hypotension: Defined as a mean arterial pressure (MAP) below 55 mmHg, requiring continuous infusion of vasopressors to maintain blood pressure.
- Severe respiratory depression: Defined as oxygen saturation dropping below 90%, necessitating airway support to alleviate the condition.
- Anaphylactic shock.
- Re-sedation after awakening: Defined as a reduction in RASS score of ≥1 point.

In the event of any of the above adverse events, the bedside physician has the authority to suspend the participant's involvement in the study. Such incidents will be recorded and reported to Ethics Committee of the First Affiliated Hospital of Xi'an Jiaotong University, with submission completed within 24 hours.

To evaluate these adverse events, the following methods will be employed: 1. Observation and Recording: A dedicated data collection form will be utilized to systematically record the occurrence, nature, and severity of each adverse event. 2. Standardized Assessment Scales: The Modified Observer's Assessment of Alertness/Sedation (MOAA/S) scale will be used to assess the level of sedation in patients. The Aldrete scoring system will be employed to evaluate recovery status post-anesthesia. 3. Regular Monitoring: Patients will be monitored every 5 minutes for vital signs and sedation levels to identify any adverse events promptly.  The proportion of participants who experienced at least one adverse event will be analyzed using appropriate statistical methods, such as the chi-square test, the chi-square test with continuity correction, or the Fisher exact test, depending on the data distribution.

All recorded adverse events will be reported in trial publications, and standardized terminology from the Medical Dictionary for Regulatory Activities (MedDRA) will be used to ensure appropriate grouping of similar harms for analysis and reporting.

**Participant timeline {18}**

The schedule of enrollment, interventions, and assessments is summarized in Figure 2 (SPIRIT Figure).

NS, normal saline; T0, intravenous sufentanil; T1, remimazolam or etomidate administration; T2, loss of eyelash reflex; T3, procedure start; T4, procedure end/flumazenil or saline injection; T5, recovery; T6, discharge from PACU.

**Sample size {19}**

This study employs a superiority design, with the minimum clinically important difference (MCID) for awakening time set at 40% based on previous literature [38]. In a pilot study involving 40 patients, an average difference in awakening time of 3.96 minutes was observed, with a 95% confidence interval of [6.07, 2.85]. Consequently, the predefined superiority margin (δ) is set at 2.83 minutes. This study hypothesizes that the combination of toremifene sodium and flumazenil will reduce anesthesia awakening time by more than 2.83 minutes in elderly patients undergoing prostate biopsies, using etomidate as a positive control. We set a one-sided significance level (α) of 0.025 and a power (1–β) of 80%, with a participant ratio of 1:1 between the experimental and control groups. Based on the results of the pilot study, the average awakening time for etomidate is 7.09 minutes (SD 4.098), while the average awakening time for the combination of remimazolam and flumazenil is 3.13 minutes (SD 1.413). To achieve the specified level of significance, a total of 236 participants will be recruited (118 in the experimental group and 118 in the control group). Considering a potential loss rate of 5%, the total planned enrollment is 250 participants (125 in each group).

**Recruitment {20}**

All participants will be recruited during their hospital stay, from admission until the time of surgery. Patients scheduled to undergo transrectal ultrasound-guided transperineal prostate biopsy will be considered potential candidates. Anesthesiologist A will meet with the patients and their legally authorized representatives (according to the laws of the People's Republic of China) prior to surgery to conduct a brief screening assessment. If the patient meets all inclusion criteria, the purpose, benefits, and risks of the clinical trial will be explained in detail to both the patient and their legally authorized representative. If the patient and their representative consent to participate, a written informed consent form must be completed. For patients who are too ill or unable to sign the consent form independently, consent will be obtained from their legally authorized representatives.

**Assignment of interventions: randomisation**

**Sequence generation: who will generate the sequence {21a}**

The specific allocation sequence will be generated by an independent statistician using SAS 9.4 software (via DATA STEP and PROC PLAN procedures), adhering to the specific design principles.

**Sequence generation: type of randomisation {21b}**

Participants will be randomly assigned to either the remimazolam group (R group) or the etomidate group (E group) in a 1:1 ratio using a block randomization method. Variable-length blocks (4/6/8 mixed) will be employed to ensure that half of the participants within each block are assigned to the remimazolam group and the other half to the etomidate group.

**Allocation concealment mechanism {22}**

In this study, allocation concealment will be achieved using the envelope method. Pharmacy personnel (not involved in the recruitment, screening, enrollment, or assessment of subjects) will be responsible for filling out the randomization allocation information in a predetermined order and placing it into envelopes marked with a unique identifier. All envelopes will remain sealed to ensure that their contents are not disclosed during the allocation process. At the time of participant enrollment, the administering anesthesiologist (Anesthesiologist B) will randomly select a sealed envelope and open it to determine the participant's group assignment. Anesthesiologist B will administer the corresponding medication based on the allocation information indicated in the envelope.

**Implementation {23}**

In this study, the personnel responsible for enrolling participants (Anesthesiologist A) will not have access to the random allocation sequence. The randomization allocation information will be securely managed by pharmacy personnel who are not involved in the recruitment or assessment of participants. Anesthesiologist B, who administers the intervention, will only access the random allocation sequence at the time of participant enrollment by selecting a sealed envelope that contains the group assignment.

**Assignment of interventions: blinding**

**Who will be blinded {24a}**

Due to the differences in appearance and dosing between remimazolam (powder formulation) and etomidate (white emulsion), this study will employ a single-blind design. Blinding will be applied to patients and research personnel, including the anesthesiologist A who screens patients preoperatively, the anesthesiologist C who collects postoperative data, the researchers responsible for follow-up and statistical analysis, and PACU nurses. Anesthesiologist B, who administers the drugs, will not participate in the blinding procedure.

**How will be blinding be achieved {24b}**

To achieve blinding in this study, remimazolam (powder formulation) and etomidate (white emulsion) will be presented in an indistinguishable manner using opaque syringes and standardized infusion

devices.

**Procedure for unblinding if needed {24c}**

- Normal Unblinding: Once all case report forms have been entered and verified for accuracy, the data manager will prepare a database verification report. Unblinding will occur after data locking, at which point the statistical analysis team will conduct the statistical analysis.
- Emergency Unblinding: In the event of an emergency (such as a severe adverse event), when it is necessary to know which treatment the participant has received for rescue purposes, an emergency unblinding procedure may be initiated. Appropriate actions will be taken based on the patient's group assignment. The responsible study personnel will complete an unblinding record form, and subsequent unblinding information should be documented in the corresponding source medical records and case report forms (CRFs). All unblinded cases will be treated as dropouts.

**Data collection and management**

**Plans for assessment and collection of outcomes {25a}**

1. Primary Endpoint (recovery time):

Anesthesiologist B and the anesthesia assistant will record the exact time when the infusion of the study drug is stopped and the administration of the antagonist or physiological saline is completed. Anesthesiologist C and the anesthesia nurse will call the patient's name every 15 seconds and will document the time of the patient's first eye opening.

2. Secondary Endpoints:

- Time to Successful Induction of Anesthesia: Anesthesiologist B and the anesthesia assistant will record the exact time of drug administration and the corresponding time when the corneal reflex disappears.
- PACU Length of Stay: PACU nurses will use the modified Aldrete scoring system to evaluate patients regularly, documenting scores until discharge criteria are met.
- DSST Scores: Anesthesiologist A will explain the DSST completion rules to the patients preoperatively and will administer the test. Anesthesiologist C will re-administer the DSST at 30 minutes and 60 minutes post-anesthesia.
- Patient Satisfaction: Patients will complete a satisfaction questionnaire prior to discharge, and study personnel will collect their responses.
- Safety Indicators: Vital signs (heart rate, non-invasive blood pressure) will be monitored using patient monitors to assess the incidence of respiratory depression and hypotension.
- Incidence of Injection Pain and Myoclonus: If patients experience these adverse reactions during anesthesia, Anesthesiologist B and the anesthesia assistant will record the occurrences.

- Incidence of Re-sedation: PACU nurses will evaluate and record the RASS score every 10 minutes during the PACU stay, as well as reassess and record it before leaving the PACU and 2 hours post-discharge.
- Incidence of Nausea and Vomiting: Anesthesiologist C and the anesthesia nurse will document any occurrences of nausea and vomiting during the perioperative period, along with the administration of antiemetics.

3. Questionnaires and Scales:

- DSST Scores: This is a validated and widely used assessment tool for psychomotor function, known for its strong reliability and validity.
- ASA Physical Status Classification: This standardized system evaluates preoperative comorbidities of patients.
- RASS Scores: The Richmond Agitation-Sedation Scale is one of the primary tools for assessing sedation levels in patients, with proven reliability in clinical practice.
- ISAS: This tool is widely used to evaluate patient satisfaction regarding their anesthesia experience.

**Plans to promote participant retention and complete follow-up {25b}**

As this study is a single-visit trial, the participant retention strategy focuses primarily on ensuring completion of the study process after randomization.

Pre-Withdrawal Prevention Strategy: The research protocol has been fully integrated into the comfortable clinical pathway for prostate biopsy, minimizing additional burdens on participants and thereby reducing the likelihood of withdrawal. The clinical team will emphasize the importance of completing the study process for both clinical care and research integrity and will address any last-minute concerns that participants may have.

Data Collection Plans: We will adhere to the intention-to-treat principle for the primary analysis. All randomized participants will be included in the full analysis set (FAS) and analyzed according to their original group assignments, regardless of any protocol deviations or withdrawals. For any participants deviating from the study protocol (e.g., receiving rescue sedation or withdrawing consent after the procedure has commenced but before data collection is complete), we will collect and retain all available data up to the point of deviation or withdrawal, including all baseline data, any data recorded during the procedure, and the reasons and nature of the deviation or withdrawal.

**Data management {26}**

Before the commencement of the study, an electronic case report form (eCRF) will be established, which will feature password-protected access to ensure data security. This system will be used to record all patient data collected throughout the trial. Each enrolled participant will be assigned a unique identification number, and essential information—including the study identifier, participant identification

number, date of the participant information form, and consent form—will be accurately documented in the eCRF.

To promote data quality, the following procedures will be implemented:

Data Entry: Data will be entered into the eCRF by trained research personnel. A double data entry process will be used to minimize errors; two separate personnel will enter the data independently, and discrepancies will be resolved through cross-examination by the data manager.

Data Coding and Security: All identifiers will be replaced with anonymous codes to protect participant confidentiality. Access to the data will be restricted to authorized personnel only, and data will be encrypted during storage and transmission.

Data Quality Assurance: Range checks will be performed for all data values to identify any outliers or entry errors promptly. Regular audits will be conducted by an independent data monitoring committee (IDMC) on a quarterly basis to ensure the integrity, accuracy, and reliability of the data collected.

Archiving of Original Data: Original data will be archived following the guidelines set out in the Good Clinical Practice (GCP) for clinical trials. The data lock will be implemented only after all quality assurance processes have been completed, ensuring that the data set is finalized and ready for analysis.

**Confidentiality {33}**

All personal information about potential and enrolled participants will be treated confidentially and managed in accordance with the Data Protection Act, NHS Caldecott Principles, the Governance Framework for Health and Social Care Research, and the conditions approved by the relevant research ethics committee.During the study, data collected will be strictly confidential, with access limited to authorized members of the research team. All documents containing participant information will be securely stored in locked cabinets designated for the anesthesia department.Accessing or deleting any data will require authorization from the principal investigator. Each participant will be assigned a unique identification number, and their details will be stored in a secure database. This database will be maintained by authorized research personnel, and only the principal investigator will have access to the complete data set. Anonymized trial data will not be shared with other researchers to further ensure participant confidentiality.

**Statistical methods**

**Statistical methods for primary and secondary outcomes {27a}**

The statistical analysis plan will include descriptive and inferential analyses. Except for the hypothesis test of the primary endpoint, which will be one-sided, all other tests will be two-sided.

1. Descriptive statistics: (1) Continuous variables will be summarized as mean ± SD for approximately normally distributed data, or as median and interquartile range (IQR) for non-normally distributed

data. Normality will be assessed using the Shapiro–Wilk test. (2) Categorical variables will be summarized as counts and percentages.

2. inferential analyses.

- Primary endpoint analysis

The primary outcome (recovery time) will be compared between groups using a one-sided independent-samples t-test. If the variances between groups are unequal, Welch's t-test will be applied; homogeneity of variance will be assessed using Levene's test. A P value < 0.025 will be considered statistically significant, and corresponding 97.5% one-sided confidence intervals (CIs) will be reported.

In addition, a generalized linear model (GLM) with a gamma distribution and log link will be used to perform covariate-adjusted analyses of recovery time, including age, ASA physical status, and procedure duration as covariates. This model will serve as a sensitivity analysis to verify the robustness of the primary analysis.

- Between-group comparisons

Multiple study endpoints will be compared between groups. Given that performing multiple independent tests on several endpoints may inflate the family-wise error rate, and that correlations may exist among variables, we plan to first conduct multivariate analysis of variance (MANOVA) using Hotelling's $T^2$ on a set of related continuous outcomes (e.g., recovery-related measures at different time points) before performing pairwise comparisons.If MANOVA indicates a significant overall group difference, subsequent between-group comparisons will be conducted for each individual endpoint. If the distributional assumptions of MANOVA are clearly violated, we will proceed directly with univariate comparisons and apply appropriate multiple-comparison adjustment methods.For continuous variables, independent-samples t-tests will be used when normality and homogeneity of variance assumptions are satisfied; otherwise, the Mann–Whitney U test will be applied. For categorical variables, the chi-square test or Fisher's exact test will be used as appropriate.

- Repeated measures

DSST scores will be analyzed with repeated measures ANOVA; Greenhouse–Geisser correction will be applied if sphericity is violated. Bonferroni post hoc tests will be conducted.

All statistical analyses will be performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). Unless otherwise specified, two-sided P values < 0.05 will be considered statistically significant.

**Who will be included in each analysis {27b}**

For the primary analysis, the intention-to-treat (ITT) population will include all randomized participants, regardless of whether they completed the study. A per-protocol (PP) population will be utilized for sensitivity analysis, comprising only those participants who adhered to the study protocol.

**How missing data will be handled in the analysis {27c}**

Statistical analysis will be conducted based on the ITT principle to ensure that all randomized participants are included in the analysis, regardless of protocol adherence. Initially, the frequency and patterns of missing data for all variables will be assessed to understand the potential impact of missing data. If the proportion of missing values for any variable exceeds 5%, multiple imputation will be used to handle missing data, enhancing the reliability and validity of the analysis. Multiple imputation is advantageous as it effectively compensates for missing data and reduces bias, providing more robust estimates. As a sensitivity analysis, a complete case analysis will also be conducted to compare the results with and without imputation, thereby evaluating the robustness of the analysis in the presence of missing data.

**Methods for additional analyses (e.g. subgroup analyses) {27d}**

For the continuous outcome of recovery time, GLMs with a gamma distribution and log link will be used for univariable and multivariable regression analyses to evaluate the associations of baseline characteristics (e.g., age, BMI, ASA physical status), perioperative factors (e.g., anesthesia/surgery duration), and the intervention with recovery time. Results will be presented as exponentiated regression coefficients (time ratios) with corresponding 95% CIs, providing covariate-adjusted estimates and sensitivity analyses for the primary outcome.
For binary safety outcomes (e.g., hypotension, bradycardia, respiratory depression, and PONV), univariable and multivariable logistic regression models will be used to assess the association between treatment group and the occurrence of adverse events. Results will be reported as odds ratios (ORs) with 95% CIs.

**Interim analyses {28b}**

1. Rationale

Previous meta-analysis[35] has shown no significant difference in recovery time (defined as eye opening) between remimazolam–flumazenil and propofol. However, several recent clinical trials reported significantly shorter eye-opening and discharge times with remimazolam plus flumazenil compared with propofol. For instance, Lee et al. found that, in breast surgery under non-intubated general anesthesia, remimazolam plus flumazenil significantly shortened eye-opening and discharge times compared with propofol[29]. Another study in outpatient surgical abortion reported shorter eye-opening and verbal response times, with psychomotor recovery non-inferior to propofol[30]. Further study in catheter ablation also indicated faster recovery with remimazolam plus flumazenil[38]. As no clinical data exist comparing remimazolam–flumazenil with etomidate, a pilot study was conducted, which showed that remimazolam plus flumazenil significantly shortened eye-opening time compared with etomidate (MD = –3.96 min, 95% CI –6.07 to –2.85). To balance efficiency and participant protection, a single interim analysis is planned.

2. Design

Number of analyses: Two (one interim analysis and one final analysis).

Timing: Interim analysis will be conducted when 50% of patients (n=125, 63 per group) have completed follow-up.

Alpha spending (O'Brien–Fleming): Interim α = 0.0013 (Z=3.000); Final α = 0.0245 (Z=1.969). No sample size re-estimation is required.

3. Stopping rules:

Efficacy stopping: Trial will stop early if, at interim analysis, the remimazolam group has significantly shorter recovery time than the etomidate group (P<0.0013) and the difference exceeds the pre-specified superiority margin of 2.83 minutes.

Futility stopping: If the observed effect is unlikely to achieve statistical significance at final analysis.

Safety stopping:The predefined safety stopping rules are summarised in Table X.

4. Implementation

The interim analysis will be conducted by the IDMC, comprising anesthesiologists, statisticians, and ethicists independent of the study team. Before analysis, the database will be locked, and only the IDMC will have access to unblinded treatment assignments. The IDMC will review recruitment, data quality, adherence, safety events, and efficacy data, and make recommendations on continuation, modification, or termination. Results will be communicated to the principal investigator within 24 h of the IDMC meeting. The detailed timeline of the interim analysis process is summarized in Table Y.

**Protocol and statistical analysis plan {5}**

After the primary trial results are published, de-identified participant-level data and the statistical code used for analysis will be made available to researchers upon reasonable request. Data sharing requests should be sent to the corresponding author, Professor Yaomin Zhu (yaomin_zhu@126.com). These requests will be reviewed by the Trial Steering Committee. Upon approval for scientific research purposes, access will be granted after signing a data use agreement, which will include commitments to use the data solely for the agreed purposes, to adequately protect the data, and not to attempt to re-identify participants. Additionally, the complete study protocol will also be available upon request.

**Oversight and monitoring**

**Composition of the coordinating centre and trial steering committee {3d}**

The coordinating centre for this trial will consist of all members of the research team. The principal investigator will be responsible for the overall implementation of the trial, ensuring compliance with the

protocol and regulatory requirements; the clinical research coordinator will manage participant recruitment and data collection; the data manager will oversee the data collection process to ensure data integrity and manage the data storage system.

The Trial Steering Committee will be chaired by Professor Yaomin Zhu, meeting quarterly to supervise trial progress, review significant decisions, ensure participant safety, and provide guidance on scientific and ethical matters.

The data management will be undertaken by Professor Pei Leilei and her team from the Department of Epidemiology and Health Statistics at Xi'an Jiaotong University. Their responsibilities include data management, development of statistical analysis plans, and final analysis to ensure the integrity and validity of the trial results.

Regarding regular meetings, the coordinating centre team will convene bi-weekly to discuss operational issues, participant enrollment, and data management; the Trial Steering Committee will meet quarterly to assess the overall progress of the trial.

**Composition of the data monitoring committee, its role and reporting structure {28a}**

An independent data monitoring committee (IDMC), comprising experts in ethics, anesthesiology, and statistics, will supervise the trial. The IDMC will review recruitment, data quality, adherence, safety events, and efficacy data and has authority to recommend trial continuation, modification, or termination. The members of IDMC declared no conflicts of interest with the sponsor or the funding party.

**Frequency and plans for auditing trial conduct {29}**

IDMC will conduct a quarterly audit of the trial via meetings or calls to ensure that the research activities are being conducted in accordance with the protocol, GCP guidelines, and applicable regulatory requirements.

**Protocol amendments {31}**

Any major modifications to the protocol by the coordinating investigator must be submitted to the First Affiliated Hospital of Xi'an Jiaotong University for approval before implementation.

**Dissemination policy {8}**

The findings of this trial will be disseminated through peer-reviewed publications, presentations at national and international conferences, and available to patients and the public through appropriate channels. Full access to the study protocol, informed consent forms, and key findings will be provided on request from the corresponding author. After the completion of the trial, the data set and statistical code will be made available upon reasonable request.

# Discussion

This is a prospective, single-center, randomized, parallel-group, superiority trial designed to evaluate the anesthetic recovery outcomes (recovery time and quality of recovery) between remimazolam combined with flumazenil versus etomidate in elderly patients undergoing transperineal prostate biopsy.

Previous studies[20], such as those by Ji et al., have shown that increasing doses of etomidate lead to progressively longer recovery times for respiration, eye opening, and orientation, and may increase the incidence of emergence agitation. This could be due to GABA receptor desensitization, which prolongs the time to synaptic blockade and cortical disinhibition[39]. In contrast, remimazolam, a novel ultra-short-acting benzodiazepine sedative, has the advantage of a specific antagonist (flumazenil), which can rapidly reverse sedation and significantly reduce recovery time. This leads our team to hypothesize that the sedation regimen of tolnazoline combined with flumazenil may have unique advantages for elderly patients undergoing daytime surgery compared to traditional anesthetic protocols primarily based on etomidate. This combination could significantly shorten postoperative awakening time, reduce the incidence of adverse reactions, and effectively facilitate the rapid and safe discharge of patients. It aligns with the core goals of the ERAS concept, which aims to reduce stress, maintain internal environmental stability, and accelerate functional recovery, potentially establishing a more efficient, safe, and patient-centered perioperative clinical pathway.

While several studies have explored the combination of remimazolam and flumazenil, there are still a few important differences worth noting: (1) To our knowledge, there are currently no clinical studies that specifically assess recovery from anesthesia using the combination of remimazolam and flumazenil compared to etomidate. Additionally, there are few clinical trials in the population of elderly patients undergoing daytime surgery, especially those undergoing prostate biopsy; (2) This study is a large-sample clinical trial that, compared to studies with smaller sample sizes, may reduce the impact of random error, allowing the results of the evaluated drug regimen to more closely reflect true efficacy. The influence of a small number of extreme values on the results of this study is relatively minor, increasing the likelihood of observing rare adverse events associated with the investigational drug regimen, and supporting the conduct of multivariate analyses to control for confounding factors. Therefore, this study aims to provide valuable evidence for optimizing anesthetic strategies in elderly patients undergoing daytime surgery.

Despite the promising results from previous studies, there are several important limitations to consider. Firstly, this is a single-center trial, which may limit the generalizability of the results to other settings. If this study demonstrates that remimazolam combined with flumazenil significantly shortens recovery times in elderly prostate biopsy patients, a subsequent multi-center, large-sample study will be planned to further confirm these findings. Secondly, this study is restricted to elderly male patients undergoing prostate biopsy, which limits the applicability of the results to other age groups, genders, or types of surgeries. Thirdly, repeated use of the DSST could potentially introduce learning effects, leading to gradually improving scores over time. To mitigate this, different versions of the DSST will be alternated randomly.

**Trial status**

The study was conducted using the latest version of the protocol and started in May 2025, with an expected duration of approximately 16 months, ending in September 2026. At the time of manuscript submission, patient recruitment had commenced, and some participants had already been enrolled.

# Abbreviations

ACLS: advanced cardiac life support

BIS: Bispectral index

BMI: Body mass index

CIs: one-sided confidence intervals

DSST: Digit Symbol Substitution Test

ECG: Electrocardiogram

ERAS: Enhanced Recovery After Surgery

FAS: full analysis set

GABA: Gamma Amino Butyric Acid

GCP: Good Clinical Practice

GLM:generalized linear model

ISAS: Iowa Satisfaction with Anesthesia Scale

ITT: intention-to-treat

IDMC: independent data monitoring committee

LVEF:Left Ventricular Ejection Fractions

METS: metabolic equivalent of task

MAP: mean arterial pressure

MOAA/S: Modified Observer's Assessment of Alertness/Sedation

MedDRA: Medical Dictionary for Regulatory Activities

MCID: minimum clinically important difference

MANOVA: multivariate analysis of variance

NIBP: Non-Invasive Blood Pressure

PONV: postoperative nausea and vomiting

PACU: Post-anesthesia care unit

PP: per-protocol

RASS: Richmond Agitation-Sedation Scale

# Declarations

**Acknowledgements**

Our team would like to thank all the patients who have participated in the trial so far, as well as all the scholars who, although not directly involved in this research design, have actively provided suggestions and support.

**Authors' contributions {3a}**

X.C. and X.Z. are the principal investigators and co-first authors of this study, contributing equally to the research; they are responsible for the research concept, protocol development, and overall trial design. Y.L., X.W., X.B., H.Y., and P.S. are involved in patient recruitment, data collection, and trial implementation. L.P. is the principal trial methodologist, participating in the statistical analysis. Y.Z., H.D., and L.P. are co-corresponding authors; they conceived and designed the study, oversaw the trial, and critically revised the manuscript for important intellectual content. All authors have read and approved the final manuscript. Authorship for future trial publications will be assigned based on individual contributions. We confirm that no professional writers were employed in the preparation of this manuscript.

**Sources of funding and other support {7a}**

This study was funded by Jiangsu Hengrui Pharmaceutical Co., Ltd. The funder had no influence on the design, implementation, or conclusions of the study.

**Availability of data and materials {6}**

Due to China's data protection laws and regulations, participant-level datasets cannot be publicly provided. If needed, please email the corresponding author to request the statistical code.

**Ethics approval and consent to participate {30}**

The Ethics Committee of the First Affiliated Hospital of Xi'an Jiaotong University approved and supported this clinical trial (XJTU1AF2024LSYY-368-03). All participants will receive written informed consent prior to enrollment. The consent process will be conducted by trained investigators using clear, non-technical language, and participants will have ample time to ask questions and consider their participation. If a participant lacks the capacity to consent, a legally authorized representative will provide consent on their behalf.

**Consent for publication**

*The informed consent materials are available from the corresponding author on request.*

**Competing interests {7b}**

The authors declare that they have no competing interests.

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# Figures

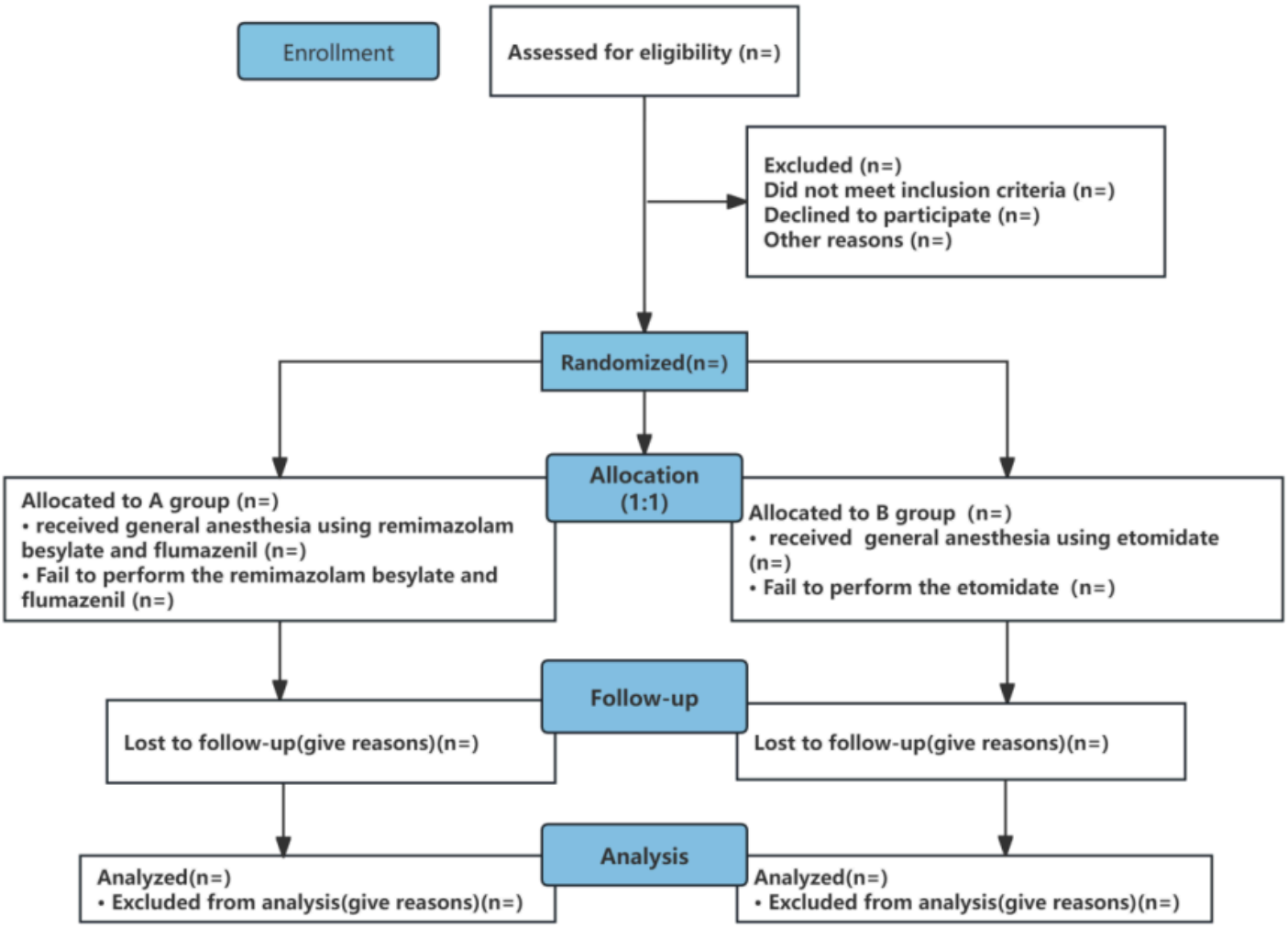



**Figure 1**

CONSORT 2010 flow diagram of the study. Agroup: remimazolam tosilate + flumazenil group; B group: etomidate group.

| STUDY PERIOD | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Enrolment | Allocation | Post-allocation | | | | | | | Close out |
| TIMEPOINT | Day -1 | day of surgery | T0 | T1 | T2 | T3 | T4 | T5 | T6 | |
| ENROLMENT | | | | | | | | | | |
| Eligibility screen | x | | | | | | | | | |
| Informed consent | x | | | | | | | | | |
| allocation | | x | | | | | | | | |
| INTERVENTIONS | | | | | | | | | | |
| sufentanil | | | x | | | | | | | |
| Remimazolam/Etomidate | | | | x | x | x | | | | |
| Flumazenil/NS | | | | | | | x | | | |
| ASSESSMENTS | | | | | | | | | | |
| Demographic data | | x | | | | | | | | |
| Hemodynamic variables | | x | x | x | x | x | x | x | x | x |
| Respiratory Parameters | | x | x | x | x | x | x | x | x | x |
| Outcome variables | | | | | | | x | | | x |
| Adverse events | | | | x | x | x | x | x | x | x |

**Figure 2**

SPIRIT figure for enrollment, intervention, and assessment schedule.

NS, normal saline; T0, intravenous sufentanil; T1, remimazolam or etomidate administration; T2, loss of eyelash reflex; T3, procedure start; T4, procedure end/flumazenil or saline injection; T5, recovery; T6, discharge from PACU.

# Supplementary Files

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- Appendices.docx