Clinical research protocol

Project approval document

Clinical study protocol for the use of escitalopram in patients with sepsis on invasive mechanical ventilation

Study type: prospective randomized controlled clinical trial

Funding: No funding

Research period: January 2025-December 2026

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Research unit: The Second Affiliated Hospital of Nanchang University

Team leader unit:

Participating units:

declaration of secrecy

team members						
number	surname and personal name	professional ranks and titles	specialty	divide the work	GCP certificate number	sign one's name
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2	Hu Weijuan	physician	emergency medicine	Scheme design, article modification	EFY-2020GCP-127	
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6						

History of program version [1]modification

Version: V 1.0 Modified time: 2024.11.07		**Version: V 1.0 Modified time: 2024.11.07**
Note: First edition		
Version: v2.0 Modified time: 2024.12.11		Version: v2.0 Modified time: 2024.12.11
chapters and sections	**Summarize the changes**	**Reasons for change**
Chapter Five	We will improve the criteria for exclusion and withdrawal	To ensure the safety of subjects and the scientific integrity of the study
Version: v3.0 Modified time: 2025.04.15		Version: v3.0 Modified time: 2025.04.15
chapters and sections	**Summarize the changes**	**Reasons for change**
Chapter Five	Improve the exclusion criteria and exclude excessive sputum secretion	Escitalopram may increase sputum production and affect the duration of mechanical ventilation
Chapter Five	Adjust the dosage of escitalopram and remifentanil	Excessive dosage of analgesic drugs has sedative effect and affects the dosage of midazolam
Chapter IX	Buy insurance for patients	Protect the rights and interests of subjects

catalogue

1、Summary of research programme

It should include research topic, research purpose, design type, research object, sample size, selection criteria, observation indicators, statistical analysis methods and other contents

Study title: Clinical study of escitalopram in patients with sepsis and invasive mechanical ventilation

Study Objective: This single-center, prospective randomized controlled clinical trial aims to compare the efficacy of escitalopram in reducing midazolam dosage, mitigating adverse effects of analgesic sedatives, and improving prognosis in patients with sepsis requiring invasive mechanical ventilation. The study seeks to confirm the safety and effectiveness of escitalopram for this population.

Design: Single-center, prospective, double-blind, randomized controlled clinical trial

Study subjects: Sepsis patients with invasive ventilation (admitted to the Emergency ICU of the Second Affiliated Hospital of Nanchang University from January 2025 to December 2026)

Number of samples: 80 (40 per group)

Inclusion criteria: Age> 18 years old, meet sepsis 3.0 criteria, need invasive mechanical ventilation
Observation indicators: 24h mean arterial pressure change before and after treatment, norepinephrine dosage, midazolam dosage, white blood cell count, platelet count, procalcitonin, IL-6, mechanical ventilation time, intestinal dysfunction incidence, delirium incidence, 28-day mortality rate, etc.

Statistical analysis methods: All continuous variables with normal or skewed distributions are presented as mean (standard deviation) or median (interquartile range), while categorical variables are expressed as percentages. For continuous variables, t-tests or Mann-Whitney U-tests are used to compare groups based on normality. Categorical variables are analyzed using Fisher's exact test or χ^2 tests. P values <0.05 are considered statistically significant. All analyses were performed using the R 3.3.2(http://www.R-project.org) and Fengrui Statistical Software V2.1.1 versions.

2、Research background information

The background, significance and current situation of domestic and foreign research are described in detail, the progress and shortcomings of the field studied in the systematic review are described, and the basis for the establishment of the research is expounded. The background information should indicate the cited references.

Sepsis is a circulatory dysfunction or failure caused by infection. When pathogens invade the body, the immune system activates to eliminate them. However, this process often damages capillary endothelium, causes capillary leakage, disrupts coagulation function, and leads to localized inflammation. Acute lung injury primarily manifests as refractory hypoxemia and respiratory distress, which may progress to severe acute respiratory distress syndrome (ARDS). This inflammatory response is characterized by reduced lung compliance and abnormal ventilation/perfusion ratio, requiring invasive mechanical ventilation to improve oxygen uptake. Such patients constitute a common category in comprehensive ICU care.

Patients on ICU mechanical ventilation (ICV) are exposed to intense stressors. During treatment, they inevitably endure various levels of harmful stimuli including counterphysiological ventilation methods, restraints, tracheal tube irritation, invasive procedures, wound care, suctioning, and environmental factors. These external stimuli, combined with the patient's underlying condition, can cause severe physical discomfort and psychological stress. This triggers anxiety, agitation, delirium, and other adverse events (1), potentially affecting clinical outcomes. For patients with respiratory failure and strong compensatory spontaneous breathing, appropriate analgesia and sedation are crucial to minimize excessive autonomic respiratory activity and prevent lung traction injuries. Effective pain management reduces metabolic rate and oxygen demand, allowing tissues to adapt to impaired oxygen supply while alleviating organ metabolic burden. This helps mitigate damage from pathological factors and buys time for functional recovery (2). Therefore, implementing proper analgesia and sedation to control disease-related stressors and avoid iatrogenic harm remains fundamental to critical care management.

Opioids, as potent central analgesics, are widely used in ICU pain management due to their strong analgesic effects, rapid onset, adjustable potency, and cost-effectiveness. However, their adverse effects primarily involve respiratory depression, hypotension, and reduced gastrointestinal motility, which are particularly pronounced in elderly patients. Therefore, the use of opioids in sepsis patients may adversely affect hemodynamic parameters and gastrointestinal function.

An ideal sedative, analgesic, or combination therapy should not only provide adequate sedation and pain relief but also demonstrate rapid onset, quick recovery after discontinuation, minimal systemic accumulation, and negligible circulatory effects. It should also exhibit anti-anxiety and anti-delirium properties (3). Ketamine, a widely used anesthetic with excellent sedative and analgesic effects, saw reduced clinical use in the late 1990s due to adverse reactions like postoperative nightmares and extrapyramidal syndrome. Escitalopramine, the pure dextrorotatory enantiomer of ketamine, is clinically utilized for analgesia and anesthesia by non-competitively inhibiting N-methyl-D-aspartate (NMDA) receptors. Its analgesic, sedative, and anesthetic effects are dose-dependent, with rapid onset and relatively short duration (4). When combined with benzodiazepines, it significantly reduces the risk of psychiatric reactions during recovery. For mechanically ventilated patients with hemodynamic instability, analgesic-sedative agents often exacerbate hemodynamic instability. Escitalopramine counteracts this by inhibiting sympathetic terminal reuptake of norepinephrine, inducing an adrenergic hyperactivity that increases norepinephrine concentration in the circulatory system, thereby producing sympathomimetic effects. Additionally, escitalopramine does not suppress respiratory drive, allowing patients to regain spontaneous breathing earlier and accelerate weaning. Furthermore, it exhibits immunomodulatory properties by reducing inflammatory cytokine levels, improving prognosis in septic patients (5,6). Therefore, escitalopram may have advantages in

improving hemodynamics, reducing respiratory depression and gastrointestinal adverse reactions in septic patients with invasive mechanical ventilation.

Escitalopram is currently only used for anesthesia induction during surgery, postoperative analgesia and painless procedures, as well as as an adjunctive treatment for depression, with limited sample size and few reported cases. There are currently no similar reports on its use in sepsis, so its efficacy and safety need to be further validated in randomized prospective clinical studies.

reference documentation ：

1.Shehabi Y, Chan L and Kadiman S, et al: Sedation depth and long-term mortality in mechanically ventilated critically ill adults: a prospective longitudinal multicentre cohort study. Intensive Care Med 39: 910-918. 2013.

2. Chinese Medical Association, Critical Care Medicine Branch: Guidelines for Pain and Sedation Therapy in Patients in Intensive Care Units with Strengthened Treatment (2006). Chinese Journal of Surgery 44:1158-1166.2006.

3. Chinese Medical Association, Critical Care Medicine Branch: Guidelines for Analgesia and Sedation in Adult ICU. Chinese Journal of Critical Care Medicine 30:497-514.2018.

4.Goyal S and Agrawal A: Ketamine in status asthmaticus: A review. Indian J Crit Care Med 17: 154-161. 2013.

5.Wang WF, Liu S and Xu B: A study of the protective effect and mechanism of ketamine on acute lung injury induced by mechanical ventilation. Eur Rev Med Pharmacol Sci 21: 1362-1367. 2017.

6.Zhang J, Ma L and Hashimoto Y, et al: (R)-Ketamine ameliorates lethal inflammatory responses and multi-organ injury in mice induced by cecum ligation and puncture. Life Sci 284: 119882. 2021.

3、Study purpose and endpoint

1. purpose of research ：

(1) Main objective: To evaluate the effectiveness and safety of escitalopram in sedation and analgesia for patients with septic mechanical ventilation, improve hemodynamic status, reduce the use of vasoactive drugs, optimize the analgesic and sedative treatment regimen, thereby shorten the duration of mechanical ventilation, reduce the incidence of gastrointestinal dysfunction and delirium, and ultimately improve patient survival.

(2) Secondary objectives: To investigate the hemodynamic stabilizing effects of escitalopram in mechanically ventilated septic patients, assessing its impact on blood pressure by monitoring 24-hour mean arterial pressure changes before and after treatment; to analyze the effect of escitalopram on norepinephrine dosage in these patients, exploring its potential advantages in reducing adrenergic drug dependence; to study the modulatory role of escitalopram on midazolam dosage and evaluate its value in optimizing analgesic and sedative regimens; to observe the incidence of intestinal dysfunction in septic patients receiving mechanical ventilation, investigating its potential benefits in maintaining organ function; to examine the influence of escitalopram on delirium rates in mechanically ventilated septic patients, analyzing its possible role in improving mental status; and to assess the effects of escitalopram on inflammatory markers (white blood cell count, platelet count, procalcitonin, IL-6, etc.) in septic patients, exploring its role in regulating immune responses.

2.End of study

(1) Key endpoints and definitions: Mechanical Ventilation Time (MVT): Type of variable: Continuous variable. Statistical measures: Final values, expressed as median (Med) and interquartile range (IQR). Time frame: Duration from initiation to discontinuation of mechanical ventilation. Clinical significance: Shortening MVT reduces complications such as pulmonary infections associated with prolonged ventilation, while also decreasing healthcare resource consumption.

(2) Secondary endpoints and definitions:

- 1. 24-hour mean arterial pressure (MAP) variation before and after treatment: Type of variable: Continuous variable. Statistical measures: Changes in baseline values, expressed as median (Med) and interquartile range (IQR). Time points: Pre-treatment and 24-hour post-treatment. Clinical significance: Hemodynamic stabilization is critical for sepsis management, as MAP variations directly reflect improvements in circulatory status.
- 2. Norepinephrine dosage: Type of variable: Continuous variable. Statistical measure: Final value, expressed as mean ± standard deviation ($\bar{x}\pm s$). Time period: During treatment. Clinical relevance: As a commonly used vasoactive agent, reducing norepinephrine dosage decreases patients' dependence on such medications. This not only helps minimize drug side effects but also reduces treatment costs.
- 3. Midazolam dosage: Variable type: Continuous variable. Statistical measure: Final value, expressed

as mean ± standard deviation ($\bar{x} \pm s$), time point: Throughout the treatment period. Clinical relevance:

As a commonly used sedative, changes in midazolam dosage can reflect the synergistic effect of escitalopram in analgesic and sedative therapy, providing guidance for optimizing analgesic and sedative regimens.

- The 4.28-day case fatality rate was used to evaluate the effect of escitalopram on survival in patients with septic mechanical ventilation by comparing the mortality rates of the treatment group and the control group within 28 days. This was a categorical variable expressed as a percentage (%) at the time point of 28 days after treatment.
- 5. Incidence of intestinal dysfunction: Variable type: categorical variable. Statistical measure: Proportion (%) (percentage). Time point: During treatment. Clinical relevance: Intestinal dysfunction is one of the common complications in septicemia patients. The reduction of its incidence can improve patient prognosis, reduce hospitalization time and medical costs.

  6. Delirium incidence: Variable type: categorical variable. Statistical measure: Proportion (%) Time point: During treatment. Clinical relevance: Delirium is a common psychiatric complication in septic patients, and the reduction of its incidence can improve patients' mental state and improve their quality of life.

  7. White blood cell count, platelet count, procalcitonin, and IL-6: Variable type: Continuous variables.

  Statistical measures: Changes from baseline values expressed as mean ± standard deviation ($\bar{x} \pm s$).

  Time points: Pre-treatment and post-treatment. Clinical significance: These inflammatory markers reflect the immune response status in septicemia patients, aiding in evaluating the role of escitalopram in modulating immune responses.

(Include specific continuous/ categorical variables, transformation values (e.g. change from baseline, final value, to endpoint

The time of occurrence of the event, etc.), statistics (e.g., median, proportion), and time points for each outcome measure; and an explanation of the clinical relevance of the selected efficacy/safety outcome measures)

4、 research design

1. Overall study design (a description of the trial design, including types such as parallel groups, crossover, factorial, and single-arm, along with allocation ratios and study categories like superiority, equivalence, non-inferiority, exploratory, etc.). For example: *****population***** *****intervention***** multi/single-center, randomized, double-blind, parallel-group controlled study)

This single-center, randomized, single-blind, parallel-group controlled study was designed to evaluate the efficacy and safety of escitalopram in sedation and analgesia in patients with septic mechanical ventilation.

Type of trial design: Parallel group control design. Subjects were randomly assigned to the experimental and control groups to ensure that the two groups were comparable in baseline characteristics.

The distribution ratio is 1:1, that is, the number of subjects in the experimental group and the control group is equal.

Blind method: double-blind design, where neither the subjects nor the investigators nor the evaluators know the grouping information to avoid selection bias and evaluation bias.

Study Type: Efficacy Study. This study evaluates whether the escitalopram combined with midazolam regimen demonstrates superior clinical outcomes compared to remifentanil combined with midazolam, by comparing differences in primary endpoints (e.g., mechanical ventilation duration) and secondary endpoints (e.g., changes in inflammatory markers, occurrence of intestinal dysfunction, and delirium).

Study subjects: Patients who meet the diagnostic criteria for sepsis and require mechanical ventilation support.

Grouping method: Patients were randomly divided into the experimental group (escitalopram combined with midazolam) and the control group (remifentanil combined with midazolam) by using a random number table.

intervention study ：

Experimental group: escitalopram and midazolam were given for sedation and analgesia.

2. Control group: given remifentanil combined with midazolam for sedation and analgesia.

5、Research plan and technical route

It includes the calculation of sample size, inclusion and exclusion criteria, evaluation indicators and methods of research results, statistical analysis plan, informed consent, ethics and other contents

1. Study population screening

(1) Selection criteria: admitted to the Emergency ICU of the Second Affiliated Hospital of Nanchang University, aged>18 years old, and in need of mechanical ventilation according to the 3.0 standard of sepsis.

(2) Exclusion criteria: ① Age <18 years; ② Pregnant or breastfeeding women; ③ Moderate-to-severe abnormal liver function (Child-Pugh grade C or higher); ④ Moderate-to-severe renal dysfunction (Scr>178 μmol/L, urea nitrogen>9 mmol/L); ⑤ History of delirium, cognitive impairment, or other psychiatric disorders prior to ICU admission; ⑥ Allergy to opioids or benzodiazepines; ⑦ Patients at high risk of severe blood pressure or intracranial hypertension: poorly controlled or untreated hypertension (resting systolic/diastolic blood pressure>180/100 mmHg), preeclampsia, or eclampsia; ⑧ Significant ischemic heart disease; ⑨ Severe pulmonary insufficiency; ⑩ Excessive sputum production.

(3) Exit Criteria: ① Participants or their families request withdrawal; ② The participant's condition significantly deteriorates during the trial, such as worsening sepsis or developing multiple organ dysfunction syndrome (MODS); ③ Poor adherence to study protocols; ④ Emergency surgeries or hospital transfers are required during the trial; ⑤ Occurrence of severe adverse reactions; ⑥ Trial suspension or overall termination; ⑦ Participant dropout.

2. Research groups

(1) Randomized grouping: Patients were randomly assigned to the trial group (escitalopram and midazolam) or the control group (remifentanil and midazolam) using a central randomization system or sealed envelope method.

3. Blind method and unblinding

(Who is blinded (e.g., subjects, healthcare providers, outcome assessors, data analysts) after the intervention is implemented, how the blinding is performed, under what circumstances the blind can be removed, and the procedures for emergency removal of the blind during the trial)

In this study, a double-blind design was employed, with the following groups remaining blinded: Subjects:

Participants were unaware whether they received escitalopram combined with midazolam or remifentanil combined with midazolam. Healthcare providers (intervention deliverers): Medical staff administering medications were unaware of participants 'specific treatment regimens. Outcome assessors: Researchers evaluating primary and secondary endpoints were not informed about participants' group assignments. Data analysts: During data analysis, analysts remained unaware of the actual treatment allocations across groups.

Implementation of the Blinding Method: Drug Preparation: The medication is packaged and labeled by independent pharmacists or professionals to ensure complete consistency between the experimental and control groups in appearance, dosage form, color, and taste. Each dose is assigned a unique random number determined by a computer-generated sequence. The packaging displays only the number, not the specific drug name. Grouping and Drug Distribution: Participants are enrolled using random numbers, with healthcare staff distributing medications based on these numbers without either party knowing the corresponding drugs. Random numbers and treatment group information are stored in sealed secure locations by designated personnel or teams until study completion. Maintaining Blindness: All participants must strictly adhere to blinding protocols throughout the study to prevent any potential disclosure of group information. For possible drug side effects, methods such as partial information disclosure or "active placebo" are employed to avoid participants guessing their group assignments through adverse reactions.

Blinding Conditions: Formal Blinding: Conducted upon study completion when all data collection and analysis are finalized, to clarify specific treatment regimens across groups. Emergency Blinding: Permitted under the following urgent circumstances: When a subject experiences a serious adverse event (SAE) requiring identification of the specific therapeutic agent for emergency management; or when a subject has overdosed or developed severe drug interactions with other medications.

Emergency Unblinding Protocol: The research site shall maintain sealed emergency letters containing participants 'treatment group information. In case of emergency, the principal investigator or designated healthcare personnel shall open these emergency letters to identify the participant's medication and immediately implement appropriate measures. All emergency unblinding actions must be documented in the Case Report Form with a detailed explanation of the unblinding rationale.

4. search procedure

(1) Study period (Describe the intervention in each group, including how and when the intervention was given; it is strongly recommended to include a study schedule, which should include screening, treatment and follow-up periods)

This study was divided into two groups, each receiving the following interventions: Both groups administered midazolam (5mg/1ml vial, Jiangsu Enhua Pharmaceutical) via intravenous target-controlled infusion for sedation. The loading dose was 0.05mg/kg administered intravenously over 2 minutes, with a maintenance dose of 0.03-0.2mg/kg·h. Sedation targets were set at RASS scores-2 to 0 points, with assessments conducted every 4 hours and dosage adjustments based on scoring results.

Experimental group: intravenous infusion of escitalopram (50mg/2ml* vial, Jiangsu Hengrui Pharmaceutical) 0.15~0.25mg/kg·h for analgesia. The analgesic target was COPT <3 points, and the dose of escitalopram was adjusted according to COPT score.

Control group: Rifenexine (1mg* branch, Yichang Renfu Pharmaceutical) 0.05~0.2ug/kg·min was administered intravenously for analgesia. The analgesic target was COPT <3 points, and the dose of Rifenexine was adjusted according to COPT score.

Implementation of interventions

Administration time: from the time when the patient is enrolled in the study and begins mechanical ventilation until the end of mechanical ventilation.

Administration: All drugs are administered by intravenous infusion, which is operated by professional medical staff.

Dosage adjustment: The dose should be adjusted by the attending physician according to the patient's sedation and analgesia effect and tolerance. Medical staff should closely monitor the patient's vital signs and consciousness status to ensure the safety and comfort of the patient.

Research schedule:

time point	Screening period	stage of therapy	follow-up period
Before entry	Participants were screened, informed consent was signed, and baseline assessment was performed		
After joining		Start mechanical ventilation and give appropriate interventions	
During treatment		Monitor the vital signs, sedation and analgesia effect, and drug dosage adjustment of patients continuously	
Mechanical ventilation is over		Record the duration of mechanical ventilation and discontinue interventions	
Day 1 of follow-up			Assess the patient's general condition and document any adverse events
Follow-up day 7			Assess the patient's

			recovery and document any adverse events
Follow-up day 28			Assess the patient's recovery and document any adverse events

(2) Research drug/treatment supply: Drugs are procured in accordance with normal hospital procedures

Administration and dose adjustment (state the criteria for discontinuation or modification of the treatment regimen in the subject, and the management of related adverse events)

The intervention measures of each group were as follows: Both groups of patients used midazolam (5mg/1ml* vial, Jiangsu Enhua Pharmaceutical) for intravenous target-controlled infusion for sedation. The loading dose was 0.05mg/kg, administered intravenously for 2 minutes, and the maintenance dose was 0.03-0.2mg/kg·h. The sedation target was RASS score-2~0 points, and the score was assessed every 4 hours to adjust the dosage of midazolam according to the score.

Experimental group: intravenous infusion of escitalopram (50mg/2ml* vial, Jiangsu Hengrui Pharmaceutical) 0.15~0.25mg/kg·h for analgesia. The analgesic target was COPT <3 points, and the dose of escitalopram was adjusted according to COPT score.

Control group: Rifenexine (1mg* branch, Yichang Renfu Pharmaceutical) 0.05~0.2ug/kg·min was administered intravenously for analgesia. The analgesic target was COPT <3 points, and the dose of Rifenexine was adjusted according to COPT score.

Implementation of interventions

Administration time: from the time when the patient is enrolled in the study and begins mechanical ventilation until the end of mechanical ventilation.

Administration: All drugs are administered by intravenous infusion, which is operated by professional medical staff.

Dosage adjustment: The dose should be adjusted by the attending physician according to the patient's sedation and analgesia effect and tolerance. Medical staff should closely monitor the patient's vital signs and consciousness status to ensure the safety and comfort of the patient.

Criteria for discontinuation or adjustment of treatment

Termination criteria: The patient develops severe hemodynamic instability, such as hypotension (systolic blood pressure <90 mmHg or 25% below baseline). The patient or his/her family requests withdrawal from the study.

Adjust the standard: adjust the dosage of drugs according to the sedation and analgesia effect and tolerance of patients. If patients have mild adverse reactions, such as bradycardia or hypotension, the dosage can be adjusted first and the reaction can be observed.

Handling of adverse events

Low blood pressure: discontinue remifentanil or escitalopram and give a 250ml fluid shock. If ineffective, ephedrine or epinephrine may be used.

Bradycardia: Discontinue infusion of remifentanil or escitalopramine and administer atropine or ephedrine as needed.

Other adverse events: according to the type and severity of specific adverse events, corresponding symptomatic treatment measures should be taken.

(3) Accompanying treatment, follow-up visits (description of relevant interventions allowed or prohibited during the trial)

Accompanying therapy permitted:

Fluid resuscitation and management: Appropriate fluid resuscitation is allowed in the initial phase of sepsis to maintain effective tissue perfusion and oxygenation, depending on the patient's specific condition. However, a restrictive fluid management strategy is recommended to reduce the risk of fluid overload.

Antibiotic therapy: The use of appropriate antibiotics for anti-infective treatment is permitted, but step-down therapy should be carried out on a daily basis to reduce unnecessary antibiotic use and reduce the risk of resistance.

Other supportive therapy: including but not limited to nutritional support, electrolyte balance adjustment, blood glucose control, etc., to maintain the basic physiological function of patients and improve the prognosis.

Prohibited concomitant therapy:

Non-study sedative analgesics: Other sedative analgesics are prohibited except for escitalopram in combination with midazolam or remifentanil in combination with midazolam as specified in the study protocol to avoid interference with the study results.

Experimental treatment without approval: The use of any experimental treatment not approved by the study protocol is prohibited.

Follow-up visits:

Life sign monitoring: including blood pressure, heart rate, respiratory rate, blood oxygen saturation, etc., to assess the patient's circulatory and respiratory function.

Assessment of sedation and analgesia effect: The effect of sedation and analgesia was assessed by observing the consciousness state, pain score and other indicators of patients.

Adverse event record: Detailed records of any adverse events that occurred during the follow-up period, including but not limited to respiratory depression, hypotension, bradycardia, etc., and corresponding treatment measures were taken.

Functional recovery assessment: Assess the recovery of organ function in patients, including lung function, kidney function, liver function, etc

(4) Patient compliance and withdrawal (Describe strategies to improve compliance with the

intervention)

Strategies to improve compliance:

Informed consent process: When signing the informed consent form, explain to the patient's family in detail the purpose, method, potential risks and expected benefits of the study. Ensure that they understand the importance of participating in the study and the possible risks.

Educational materials: Provide easy to understand written materials, including the mechanism of action, expected effects, possible adverse reactions, etc. For conscious patients, they can be directly communicated with; for unconscious patients, detailed communication with their families.

Video education: If possible, short videos can be made to show the research process and how to use the drug, helping family members better understand the research.

Cultural sensitivity: Take into account the cultural background and education level of patients and their families, and communicate in a language and manner that they can understand. For patients with less educated families, use simple and straightforward language.

Psychological support: Provide patient answers and support to the concerns and questions of patients' families, help them build confidence and reduce anxiety.

Dosage adjustment: Adjust the dosage of the drug in time according to the patient's response and tolerance to ensure that the patient is treated within a safe and effective dose range.

Feedback mechanism: Establish an effective feedback mechanism, so that patients' families can express their concerns and suggestions in time, and medical staff can make adjustments according to the feedback.

Family communication: Regular communication with family members about the treatment of patients to ensure that they can timely understand the changes in the patient's condition and the progress of treatment.

withdraw from ：

When a patient or their family voluntarily requests to withdraw from the study, their wishes should be respected. Detailed documentation of withdrawal reasons must be maintained, and alternative appropriate treatments should be ensured. If serious adverse events such as hypotension or bradycardia occur during the study and cannot be alleviated through dose adjustment or symptomatic management, interventions should be immediately discontinued, and the patient should be withdrawn from the study.

5. appraise

（1）Efficacy assessment

Main efficacy indicators

Pain and sedation effect: Use RASS and COPT scores to assess the level of pain and sedation in patients to ensure that patients maintain appropriate pain and sedation during treatment.

Secondary efficacy indicators

Dosage: Record the total dose of escitalopram, midazolam and remifentanil required to achieve the target

sedation level.

Time to wake up: The time from the discontinuation of the drug to the patient's complete awakening, and the assessment of the rate of metabolism and clearance of the drug.

Hospitalization time: Record the total hospitalization time of patients in ICU and hospital to evaluate the impact of treatment on the patient's recovery process.

Delirium incidence: The incidence of delirium was recorded using standardized delirium assessment tools (e.g., CAM-ICU).

（2）Security assessment

Major security indicators

Cardiovascular system adverse events: Record cardiovascular system adverse events such as hypotension (systolic blood pressure <90 mmHg) and bradycardia (heart rate <50 beats/min) during treatment.

Other adverse events: Other adverse events such as nausea, vomiting, allergic reactions, etc. recorded during treatment.

Secondary safety indicators

Laboratory tests: Blood routine, liver and kidney function, electrolytes and other laboratory tests were performed before and after treatment to evaluate the effects of drugs on patients' physiological functions.

Severity of adverse event: The severity of the adverse event is classified as "definitely related", "probably related", or "uncertain".

appraisal procedure

Adverse event records: During treatment and follow-up, any adverse events that occur in the patient are recorded in detail, including the time of occurrence, duration, severity, and treatment measures.

Laboratory tests: Regular laboratory tests are performed before, during and after treatment to monitor the patient's physiological indicators.

Emergency treatment: For serious adverse events, such as respiratory depression or hypotension, emergency treatment measures should be taken immediately and the treatment process should be recorded.

6. statistical analysis

（1）Sample size determination

(The number of subjects expected to be required to achieve the study objective and the calculation method should include any clinical and statistical assumptions)

The primary endpoint is "time on mechanical ventilation" (TOV), a quantitative measure. Based on literature data, we hypothesize: The average TOV for the experimental group (escitalopram + midazolam) is μ1 48 hours, while the control group (remifentanil + midazolam) has an average TOV of μ2 72 hours. The standard

deviation (σ) is 24 hours. The Type I error rate (α) is 0.05 (two-tailed). The power (1- β) is 80%.

Choose the appropriate sample size calculation formula

According to the above parameters, the following formula can be used to calculate the sample size (two groups are equal parallel 1:1 design): $n=2\ (Z\alpha/2+Z\beta)2\times\sigma2/(\mu2-\mu1)2$

Among them, Zα/2 is the two-sided α percentile of the standard normal distribution, and when α=0.05, Zα/2 =1.96. Zβ is the β percentile of the standard normal distribution, and when β=0.20, Zβ =0.84.

Calculate the sample size by substituting parameters

Substitute the above parameters into the formula: $n\approx6.84$

Since the sample size must be an integer, rounded up, at least 7 cases are required per group.

Consider the dropout rate: a certain dropout rate should be considered. Assuming that the dropout rate is 10%, the adjusted sample size is: n adjustment =n/(1−dropout rate)≈7.78, and it is rounded up to 8 cases per group.

Therefore, at least 8 cases per group and a total of at least 16 cases in the two groups were required. The sample size of this study was set at 80 cases, with 40 cases per group.

（2）Analytical population (Describe the statistical definition of the population. For subjects who did not comply with the study protocol, focus on which analysis group they were placed in and what statistical method was used to deal with the data of loss to follow-up)

a. Full analysis set: Includes all randomized participants who received at least one treatment. Participants without follow-up records after enrollment were excluded. For missing primary efficacy endpoints, previous results can be carried over. Missing values for secondary efficacy endpoints are typically not carried over but analyzed using available data.

b. Compliant participants: Those who fully followed the protocol, were well compliant, did not use prohibited drugs, and had complete baseline values for key indicators. Participants with serious protocol violations were excluded. Instead of carrying over missing values, participants with missing critical data were directly excluded.

c. Safety analysis set: This includes all enrolled subjects who received treatment, including those who discontinued medication after adverse reactions occurred during the study period. Subjects who did not comply with the study protocol are included in this analysis set. For missing safety indicators, data is typically not carried forward but directly incorporated into the available evaluation portion while excluding cases.

（3）Efficacy analysis and statistical methods

a. Analysis of primary endpoints: Mechanical Ventilation Time (MVT), defined as the duration from initiation to successful weaning. A full-analysis set was employed to ensure robustness and reliability of results. Based on data normality, paired t-tests or Mann-Whitney U-tests were used to compare MVT between groups. The statistical significance threshold was set at $P < 0.05$, with 95% confidence intervals (CIs) calculated to assess the range of differences in MVT between groups.

b. Analysis of secondary endpoints: Changes in mean arterial pressure (MAP) over 24 hours before and after treatment, norepinephrine dosage, midazolam dosage, white blood cell count, platelet count, procalcitonin levels, IL-6, incidence of intestinal dysfunction, delirium occurrence rate, and 28-day mortality rate. The primary analyses were conducted using full analysis sets and compliant protocol sets to provide more accurate efficacy assessments. For continuous variables (e.g., MAP changes, norepinephrine dosage, midazolam dosage, and inflammatory marker changes), paired t-tests or Mann-Whitney U-tests were employed based on data normality. Categorical variables (e.g., intestinal dysfunction incidence, delirium occurrence rate, and 28-day mortality rate) were analyzed using chi-square tests or Fisher's exact test, with selection determined by sample size and data distribution. A $P < 0.05$ was set as the statistical significance threshold, and 95% confidence intervals (CIs) were calculated to evaluate the range of mechanical ventilation duration differences between groups.

（4）Interim analysis (describes the criteria for interim analysis/stop analysis, including who can obtain the results of these interim analyses and the final decision to stop the trial.)

Mid-term Analysis: With a sample size of 80 cases initially planned, the interim analysis will be conducted when 40 cases (50%) are enrolled. This analysis is overseen by the Data Monitoring Committee and its findings remain confidential, being disclosed only to the sponsor and investigators if study termination becomes necessary. Final decision on trial discontinuation: The Data Monitoring Committee will recommend continuation, protocol adjustments, or termination based on interim analysis results, with the sponsor having

the final say in this matter.

（5）Data Monitoring Committee (If interim analysis is to be conducted, a data monitoring committee should be established. Please briefly describe its composition, structure and responsibilities, and state whether it is independent of the research team and whether there are conflicts of interest. If no data monitoring committee is established, explain the reasons.)

The structure of the data monitoring committee: chairperson, members and an independent statistical team. The members include senior clinicians, statisticians and ethical workers, etc., who are independent of the sponsor and the research team and have no conflicts of interest.

7. Definition of the end of study

All subjects completed the scheduled 28-day follow-up period and all data were collected.

6、 safety evaluation

1. Adverse Events: The main adverse reactions observed in pre-marketing clinical trials of escitalopram include: psychiatric disorders (agitation, delirium, separation anxiety disorder, delirium, confusion, nightmares, etc.), neurological disorders (drooling, head discomfort, tremors, etc.), ocular disorders (blurred vision, diplopia, etc.), cardiac disorders (tachycardia, elevated blood pressure, etc.), vascular disorders (hypertension), gastrointestinal disorders (nausea, vomiting, etc.), as well as injuries, poisoning, and other complications.

2. Definition of adverse event: Adverse events are defined as the occurrence of the above adverse reactions after subjects received esketamine treatment.

3. Abnormal test results: When significant deviations occur in test outcomes that contradict the patient's disease progression or show substantial discrepancies from previous results, contact the laboratory department to verify specimen reliability and conduct timely retesting. Examine for human or equipment factors to ensure accuracy. If the result remains abnormal after excluding these factors and shows a change of ±50% compared to previous results, consider the test results as abnormal.

4. Serious adverse event: The patient died during the trial, and the autopsy report indicated that it was related to escitalopram, which was a serious adverse event.

5. Severe degree assessment: adverse reactions that are life-threatening (such as organ injury, poisoning) are severe; adverse reactions that affect treatment (agitation, confusion, nightmares, tremors, heart rate +20%, blood pressure +20%) are moderate; and mild symptoms (nausea, vomiting) are mild.

6. Relevant judgment: If the above adverse events occur, excluding other factors leading to adverse reactions, it is determined to be drug-related adverse reactions.

1. Case report form/electronic data collection

1. Subject information sheet

Field number	Field name	bear fruit
001	Subject number	
002	surname and personal name	Anonymizable
003	sex	
004	age	
005	admission number	
006	Date of entry	
007	Research groups	Test group or control group

2. Baseline data table

Field number	Field name	bear fruit
101	Basal mean arterial pressure	
102	Basal white blood cell count	
103	Basal platelet count	
104	Basal procalcitonin	
105	Baseline IL-6 levels	
106	Baseline SOFA score	
107	base line BMI	

3. Treatment process table

Field number	Field name	bear fruit
201	When the medication started	
202	drug dose	
203	Dosage adjustment time	
204	Adjusted dose	
205	Start time of mechanical ventilation	
206	Time of mechanical ventilation termination	

4. Data observation table

Field number	Field name	bear fruit
301	Mechanical ventilation time	
302	Mean arterial pressure after 24 hours	
303	Go to epinephrine dosage	
304	Midazolam dosage	
305	White blood cell count after 24 hours	
306	Platelet count after 24 hours	
307	Procalcitonin after 24 hours	
308	IL-6 levels after 24	

	hours	
309	Intestinal dysfunction occurs	
310	Delirium occurs	
311	28 days to die	

5. Table of adverse events

Field number	Field name	bear fruit
401	Description of adverse event	
402	When the adverse event occurred	
403	Severity of adverse events	
404	Relationship between adverse events and treatment	
405	Measures to deal with adverse events	
406	Adverse event results	

6. Exit or suspend the table

Field number	Field name	bear fruit
501	Exit/termination date	
502	Reason for withdrawal/termination	

7. Study completion table

Field number	Field name	bear fruit

601	End date of study	
602	Research completed	
603	Reasons for early termination	

2. Data management

data sources ：

Clinical records: including medical records, laboratory test results, imaging test results, etc.

Research team records: including observation records of research nurses and research doctors.

Self-reported data: such as quality of life questionnaire.

Data collection process: Team members are responsible for data collection and preliminary review. After each data collection, another team member will review the data to ensure its accuracy and completeness.

Data entry: Use EDC system for data entry to ensure real-time and accurate data. EDC system should have automatic verification function to reduce data entry errors. The system should support multi-user simultaneous operation to ensure the efficiency of data entry.

Data entry process: Data entry personnel are trained to be familiar with the operation of CRF and EDC system. After data entry, the data administrator conducts preliminary review to ensure the integrity and consistency of the data. For problems found, they communicate with the data collection personnel in time for correction.

data cleaning

Data cleaning plan: Conduct regular data cleaning to check the integrity and consistency of data. For missing data, process them according to the research protocol and statistical analysis plan. For abnormal data, conduct sensitivity analysis to evaluate its impact on research results.

Data cleaning process: The data administrator is responsible for the specific implementation of data cleaning. The problems found in the cleaning process are recorded in the data cleaning report and communicated with the research team in time. For the data that needs to be corrected, the data collection personnel shall verify and correct it.

data storage

Data storage system: Use a secure database system to store data and ensure the confidentiality and integrity of data. The database system should have backup and recovery functions to prevent data loss.

Data storage process: Data storage should comply with regulatory requirements to ensure the privacy of subjects. The duration of data storage should be determined according to the study protocol and regulatory

requirements.

data security

Data access rights: Restrict data access rights, and only authorized personnel can access the data. Use user name and password for authentication to ensure data security.

security of data

Ensure that the personal information of the subjects is confidential and that the data does not contain any information identifying the subjects. During data transmission, encryption technology is used to protect the security of the data.

Data review

Internal audit: Conduct internal audit regularly to check the compliance of data management process. The results of internal audit are recorded in the audit report, and the problems found are rectified in time.

External audit: Accept external audit from sponsors, ethics committees and regulatory agencies. For problems found in external audit, rectify them in time and submit rectification report.

data report

Interim report: Prepare an interim report based on the interim analysis results and submit it to the Data Monitoring Committee (DMC) and sponsor.

Final report: After the completion of the study, write a final report including research results, data analysis and conclusions.

The final report is subject to review and approval by the research team.

7、Data collection and management

Viii. Quality Management Plan (Please introduce the relevant measures to ensure project quality and schedule)

1. Screening of subjects

Screening and enrollment: The screening of subjects was carried out in strict accordance with the study protocol to ensure that the enrolled subjects met the inclusion/exclusion criteria, and the informed consent was arranged.

2. Implementation and data collection phase

Implementation of the research protocol: Ensure that the research process is carried out in strict accordance with the approved protocol, including administration, follow-up, examination, etc.

Data management and quality control: Establish a data management system to ensure the accuracy, integrity and confidentiality of data. Implement regular data review and quality control checks to detect and correct problems in time.

Progress monitoring: regularly track the project progress, compare the deviation between the actual progress and the planned schedule, analyze the reasons and take corrective measures.

3. Data analysis and reporting stage

Data statistical analysis: clean, sort and analyze the data according to the statistical plan to ensure the scientificity and reliability of the analysis results.

Write a research report: Based on the data analysis results, write a detailed research report, including research background, methods, results, discussion and conclusion.

Submission of reports and review: Submit the study report to the ethics committee and regulatory authorities for review, and make necessary modifications based on feedback.

4. Project closure and follow-up

Project summary: Review and summarize the whole clinical trial project, evaluate the success and shortcomings of the project, and provide reference for future research.

File archiving: All research documents, including research protocol, ethical approval, subject data, data records, analysis reports, etc., shall be sorted and archived to ensure compliance with regulatory requirements.

Follow-up action: Formulate follow-up research plan according to the research results.

9. Pre-assessment of project risk benefits and risk control plan

Please describe the risks and benefits that may be undertaken by researchers, subjects and medical institutions when carrying out this project; if there are risks, please introduce the risk control measures and feasibility.

1. Benefit/risk evaluation:

The risks and benefits to the subject

Risk to the subject

Drug-related risks: Cardiovascular system adverse reactions: Escitalopram may cause cardiovascular effects such as increased heart rate and elevated blood pressure. Neuropsychiatric system adverse reactions: It may lead to neurological manifestations including delirium, hallucinations, and cognitive impairment. Respiratory system adverse reactions: Although the respiratory depression effect of escitalopram is relatively mild, it may still induce respiratory inhibition at high doses.

Risks in the process of research: Risks related to mechanical ventilation: Mechanical ventilation itself may bring risks such as lung injury and infection. Discomfort caused by frequent monitoring: Frequent monitoring of vital signs and laboratory indicators in the process of research may cause some discomfort to subjects.

Benefit to the subject

Potential analgesic and sedative effects: Escitalopram has a good analgesic and sedative effect, which may reduce the pain and anxiety of subjects.

Reduce opioid use: Escitalopram can reduce opioid use and reduce the incidence of opioid-related adverse reactions.

Improved prognosis: By optimizing the sedation and analgesia regimen, mechanical ventilation time and hospital stay may be shortened and the prognosis of subjects improved.

risk control measures

Strict monitoring: during the study, the subjects were strictly monitored for cardiovascular and respiratory system to detect and deal with adverse reactions in time.

Dosage adjustment: Adjust the dosage of the drug in time according to the subject's response and tolerance to avoid the risks of high dose.

Psychological support: Provide psychological support and necessary intervention for subjects with adverse neuropsychiatric reactions.

Risks and benefits to researchers

Risks of researchers: Research pressure: Researchers need to invest a lot of time and energy in research, and may face greater work pressure.

Data management risk: data loss, incorrect input and other problems may occur in the process of data collection and management, which will affect the accuracy of research results.

Researcher Benefits: Academic Contributions: This study provides new clinical evidence for sedation and analgesia management in septic ventilated patients, enhancing academic impact. Professional Development: Clinical research participation strengthens researchers' expertise in study design, data management, and statistical analysis.

risk control measures

Teamwork: Establish a professional research team with clear division of labor to reduce the pressure on individual researchers.

Data quality control: The electronic data acquisition system (EDC) is used for data management, and the data is

cleaned and reviewed regularly to ensure the accuracy and integrity of the data.

Risks and benefits of medical institutions

Risks of medical institutions: Resource input: Clinical research requires certain medical resources, including human, material and financial resources. Reputation risk: If serious adverse events or unsatisfactory results occur during the research, the reputation of medical institutions may be affected to some extent.

Benefits to medical institutions: Improve the level of medical care: By participating in clinical research, medical institutions can introduce new treatment plans and improve the overall level of medical care.

risk control measures

Rational planning of resources: Plan medical resources reasonably according to the research plan to ensure the smooth progress of the research.

Strengthen ethical review: strictly follow the requirements of the ethics committee to ensure the scientific and ethical nature of the research and reduce reputation risks.

2. morality and ethics

(1) Ethics committee (Describe how the plan was approved by the research ethics committee/institutional review board)

1). Respect the autonomy of participants

Informed consent: Ensure that participants are fully informed of the purpose, process, potential risks and benefits of the study and participate voluntarily. Provide a clear and understandable informed consent form that allows participants to withdraw at any time.

-No coercion: Avoid any form of coercion or undue influence to ensure that participants make their own decisions.

2). Risk minimization

-Risk assessment: Identify and assess the physical, psychological, social or economic risks that may be associated with the study and take measures to minimize them.

-Balance of risks and benefits: Ensure that the potential benefits of the research outweigh the risks, and that the risks are within a reasonable range.

3). Protect privacy and confidentiality

-Data protection: Take appropriate measures to protect participants' personal information, ensure data security and prevent unauthorized access or disclosure.

-Anonymization: Use anonymous or deidentified data whenever possible to avoid disclosure of participant identity.

4). Fairness and justice

-Fair selection of participants: Ensure that participants are selected fairly and without discrimination or exclusion against specific groups.

-Fair distribution of benefits: ensure fair sharing of research results and avoid uneven distribution of benefits.

5). Protection of special groups

-Cultural sensitivity: Respect participants from different cultural backgrounds and avoid cultural conflicts or offenses.

6). Research design and scientificity

-Scientific rationality: Ensure that the research design is scientific and reasonable, and avoid unnecessary research or repeated experiments.

-Ethical review: The research protocol should be reviewed by the ethics committee to ensure compliance with ethical standards.

7. Ongoing monitoring and reporting

-Ongoing supervision: Ongoing supervision during the research process to ensure compliance with ethical standards and timely resolution of issues.

-Reporting mechanism: Establish a reporting mechanism that allows participants or researchers to report ethical issues and deal with them in a timely manner

8). Ethics training

-Researcher training: Ensure that researchers receive ethical training and understand and follow ethical norms.

-Ethical awareness: Improve the ethical awareness of the research team to ensure that the research process complies with ethical standards.

9). Communication with the ethics committee

-Transparent communication: Maintain transparent communication with the ethics committee, submit research progress and changes in time to ensure compliance with ethical requirements.

-Feedback and improvement: Improve the research plan according to the feedback from the ethics committee to ensure compliance with ethical standards.

10). Ethics review documents

-Complete submission: Submit complete research plan, informed consent form, risk assessment report and other documents to the ethics committee to ensure smooth review.

-Update in time: Update the documents in time during the research process to ensure that the ethics committee is kept up to date.

（2）Patient information and informed consent (state who will obtain informed consent from the subject or guardian and how it will be obtained, as well as a clause on compensation for harm caused by participation in the trial; if data and biological specimens from the subject are to be collected and used for other research, this should be stated additionally)

In studies involving patient information and informed consent, ensuring that subjects or their guardians fully understand the study and voluntarily agree to participate is a core requirement of ethical review. The following is a detailed description of the informed

consent process and compensation clauses:

1). Acquisition of informed consent

Who is responsible for obtaining informed consent?

-Researchers or designated persons: Informed consent is usually obtained by the principal investigator (PI) or a trained research team member. These persons should have good communication skills and be able to explain the research clearly.

-Independent witness: In some cases (e.g. where the subject has limited education or language barriers), an independent witness may be required to ensure that the informed consent process is fair and transparent.

2). How to obtain informed consent?

1. Provide sufficient information:

-Explain in detail to the subject or his/her guardian the purpose, procedure, duration, potential risks and benefits, alternative treatment options, etc.

-Use language that the subject can understand and avoid technical terms.

-Provide written informed consent in a clear and concise manner.

2. Ensure understanding:

-Ask questions or give feedback to confirm that the subject or his/her guardian understands the study.

-Give the subject enough time to think and avoid making decisions under pressure.

3. Voluntary consent:

-Emphasis on full voluntary participation, and the right of participants to withdraw from the study at any time without affecting their regular treatment or interests.

-Ensure that the subject or his/her guardian signs the informed consent form without coercion or inducement.

4. Handling of special cases:

-Persons without capacity: consent of their legal guardian is required.

-Persons with language barriers: provide translation services or use an informed consent form in a language familiar to the subject.

5. Recording and Archiving:

-The informed consent form signed should be in duplicate, one copy for the subject and one copy for the research team to file.

-Record the process of informed consent (e.g. time, place, participants, etc.).

2). Compensation clauses for harm caused by participation in the experiment

In order to protect the rights and interests of subjects, this study plans to purchase clinical trial liability insurance for subjects.

insurance cover

Serious adverse events: The insurer shall be liable for the compensation of serious adverse events caused by the implementation of clinical trials or the exposure of subjects to clinical trial products, and the first claim shall be made during the insurance period or the claim grace period, and the economic compensation liability that should be borne by the insured in accordance with the laws of the People's Republic of China.
Legal costs: The insurer is responsible for the payment of legal costs incurred in the investigation, settlement or defense of a claim or lawsuit covered by the insurance.

waiver

Not approved or not qualified: the clinical trial is not approved or revoked, or the institution, service organization or investigator involved in the clinical trial does not have the corresponding qualification.

Violations of laws: The insured or the additional insured violates laws, regulations, rules or other government instructions or orders, including mandatory provisions of the Good Clinical Practice for Drug Clinical Trials and the Good Clinical Practice for Medical Device Clinical Trials.

Intentional or gross negligence: intentional act, gross negligence or illegal act of the applicant, the insured and their employees and representatives.
Unrelated actions: Losses caused by diagnosis, treatment or other actions unrelated to the clinical trial.
Unauthorized representations or warranties: additional representations or warranties made by the additional insured without the authorization of the insured.
Medical liability: medical liability of researchers and staff of the testing institution.
The product did not achieve the desired effect: The clinical trial product did not achieve the desired effect.
Original disease or unrelated health deterioration: injury, death or health deterioration due to the original disease or even if the subject does not participate in the trial.
Impact on specific population: the impact of the clinical trial product on the health of pregnant women and fetuses, except with the written consent of the insurer.
Specific viruses or lesions: viral hepatitis, lymphadenovirus, human T-lymphotropic leukemia virus and related viruses, infectious spongiform encephalopathy, and AIDS-related lesions.
Previous injury or exposure: a personal injury that the subject had prior to the start date of insurance or prior to the retroactive date, or use or exposure to the clinical trial product prior to the retroactive date.
Post-experiment use: The subject continues to use the investigational drug or equipment after the end of the clinical trial or after the trial is ordered to be temporarily stopped or interrupted.
Specific events: war, hostile action, military act, armed conflict, strike, riot, mob violence, terrorist activity; nuclear radiation, nuclear explosion, nuclear contamination or other nuclear accident; earthquake, tsunami or other natural disaster; air pollution, land pollution, water pollution or other pollution; administrative acts, judicial acts.
Specific compensation: compensation for mental damage, fines, penalties, punitive damages; all kinds of property losses and indirect losses; claims that the policyholder or the insured knew or could reasonably foresee before taking out the insurance; the liability that the insured should bear according to the agreement signed with others, except the legal liability that the insured should still bear according to law.
Other non-insurance liabilities: other losses, expenses and liabilities not covered by this contract.

Limits of compensation and deductibles

Limits of indemnity: including the cumulative liability limit of the policy and the liability limit for each clinical trial subject. Each limit of indemnity, including legal costs, shall be determined by the policyholder and the insurer through negotiation and stated in the insurance schedule.
Deductible: it shall be determined by the applicant and the insurer through negotiation when signing the insurance contract, and shall be stated in the insurance details.

adjustment of claims

Timely notification: The subject or his/her family should immediately notify the investigator or sponsor and provide relevant supporting materials after knowing the occurrence of the insured event.

Assist in investigation: The subject or his/her family members shall cooperate with the investigator or sponsor in accident investigation and provide necessary assistance.
Compensation claim: After receiving the compensation claim from the subject, the investigator or sponsor shall promptly file a claim with the insurance company and provide the original insurance policy, trial protocol, informed consent form, trial agreement and qualification certificate, case report form and disability death certificate, compensation agreement or settlement letter, technical evaluation report and other certificates and materials.
Compensation verification: After receiving the claim application, the insurance company will investigate and verify the accident, and make a compensation decision within the prescribed time.
Through the above compensation clauses, comprehensive protection is provided for the subjects to ensure that reasonable compensation can be obtained for the hazards caused by the trial during the participation of the trial.

X. Human genetic resources

Human genetic resources materials refer to the genetic materials such as organs, tissues and cells containing human genome, genes and other genetic materials. Human genetic resources information refers to the data and other information materials generated by using human genetic resources materials.

If the above content is involved, you need to fill in this section. The description includes collection category, quantity, storage conditions, whether to go abroad, whether to disclose information and other information.

Does not involve the above

11、 appendix

For example, research related standard scales, diagnostic criteria, grading criteria, etc.;

RASS grade

fraction	classify	description
+4	Aggressive	Very aggressive, violent tendencies that pose a danger to medical personnel
+3	Very agitated	Very agitated, pulled out various catheters
+2	Restlessness and anxiety	The body was moving violently and could not be coordinated with the ventilator
+1	Anxiety	Anxious and tense, but not physically active
0	Stay awake and calm	Be sober and natural
-1	be sleepy	Not fully awake, with eye contact after sound stimulation, can remain awake for more than 10 seconds
-2	Mild sedation	After sound stimulation, they can wake up and make eye contact for less than 10 seconds
-3	Moderate sedation	They can open their eyes after being stimulated by sound, but they cannot make eye contact
-4	Deep sedation	No response to sound stimulation, but can open eyes or move after pain stimulation
-5	Can't wake up	No response to sound or pain stimuli