A Multicenter Randomized Controlled Clinical Study of the Tiaoshen Anti-cancer Regimen Combined with Cognitive Behavioral Therapy in Improving Ovarian Cancer-Related Insomnia and Progression-Free Survival

I. Research Background

1. Ovarian cancer-related insomnia is highly prevalent, severely impacting patients' quality of life and long-term prognosis, and has become a bottleneck limiting the improvement of comprehensive therapeutic efficacy in ovarian cancer.

Cancer-related insomnia (CRI) refers to insomnia symptoms that occur in cancer patients either accompanying the onset of cancer or during anti-tumor treatment. It manifests as difficulty falling asleep, shallow sleep, easy awakening, excessive dreaming, and early morning awakening. The incidence of CRI exceeds 60%, leading to a significant decline in quality of life and affecting the completion of comprehensive cancer treatment, thus becoming a key factor restricting the improvement of therapeutic efficacy.

Ovarian cancer is a cancer type with a high incidence of CRI, and its insomnia issues are of great clinical concern. Compared to male cancer patients, female cancer patients are more prone to developing insomnia. The drastic hormonal fluctuations after ovarian cancer surgery, the impact of sex organ removal on patients' self-perception, and social barriers further exacerbate the occurrence of ovarian cancer-related insomnia. Additionally, ovarian cancer is characterized by high incidence and high mortality rates among female reproductive system malignancies. Approximately 70% of patients are diagnosed at an advanced stage, are prone to recurrence and metastasis, and have a low five-year survival rate. These severe clinical features impose a tremendous psychological burden on patients and are key

factors contributing to the high prevalence of insomnia symptoms. Insomnia causes multiple harms to ovarian cancer patients: it induces fatigue, reduces physical performance scores, leads to accompanying symptoms such as anxiety and depression, forming an ovarian cancer-related psycho-oncological symptom cluster that significantly reduces patients' quality of life from both physical and mental dimensions. It also reduces patients' tolerance to comprehensive treatment, exacerbates related adverse reactions, lowers the completion rate of comprehensive treatment, leads to limited survival benefits, and becomes a bottleneck for improving efficacy. In summary, insomnia forms a vicious cycle of "insomnia-progression" in ovarian cancer patients through multiple pathways, urgently necessitating the development of corresponding diagnostic and therapeutic regimens to improve comprehensive treatment outcomes.

2. Developing a comprehensive regimen for ovarian cancer-related insomnia to overcome the bottleneck in improving therapeutic efficacy.

Currently, there is a lack of comprehensive regimens specifically targeting ovarian cancer-related insomnia both domestically and internationally. Clinical practice generally draws upon management strategies for CRI, including pharmacological and non-pharmacological approaches. Among non-pharmacological treatments, Cognitive Behavioral Therapy for Insomnia (CBT-I) is recommended as a first-line therapy by domestic and international guidelines. Its core components include sleep restriction, stimulus control, relaxation training, cognitive restructuring, and sleep hygiene education. It can significantly alleviate insomnia symptoms in cancer patients, shorten sleep onset latency, reduce nocturnal awakenings, improve sleep efficiency, and has few adverse effects. Furthermore, non-pharmacological therapies such as mindfulness meditation, exercise, and music have also shown promising results. In pharmacological treatment, sedative-hypnotics are effective for short-term management of CRI; however, long-term use can lead to tolerance, dependence, and rebound insomnia, and may be associated with daytime side effects (somnolence,

decreased attention) and serious risks (infection, depression, cognitive impairment, and increased mortality risk). Newer dual orexin receptor antagonists promote sleep by blocking the arousal pathway but also have adverse reactions such as dizziness, headache, and cognitive impairment. Melatonin is increasingly used in CRI, but there is a potential risk of additive effects with adverse reactions to anti-cancer treatments (such as nausea and anorexia).

Traditional Chinese Medicine (TCM), with its patient-centered and holistic approach, holds potential advantages in the prevention and treatment of CRI. Studies have found that the classic formula Suanzaoren Tang can significantly improve CRI symptoms and may help prolong patient survival. Formulas such as Tianwang Buxin Dan and Jiawei Guipi Tang have also shown promising effects in improving insomnia. TCM therapies are unique and have demonstrated significant efficacy. The Journal of Clinical Oncology reported that the efficacy of the traditional Daoyin technique Tai Chi is comparable to the gold standard CBT-I. Acupuncture for CRI can effectively reduce insomnia symptoms, prolong sleep duration, and improve sleep quality. Characteristic therapies such as five-element music therapy, Tuina, scraping, and auricular acupoint therapy have also shown certain clinical efficacy, but all lack rigorous clinical validation.

However, the etiology and manifestations of insomnia vary across different cancers, making it difficult for a universal regimen to fully address the characteristics of ovarian cancer-related insomnia. Furthermore, existing treatments for CRI are limited to alleviating the "insomnia" symptom, with insufficient attention to the key pathogenesis of "tumor-induced insomnia." In light of this, our team has been dedicated to researching the etiology and pathogenesis of cancer-related insomnia and developing effective intervention regimens. Through integrated Chinese and Western medicine explorations, we have gradually established a "Tiaoshen Anti-cancer" research system for treating ovarian cancer-related insomnia.

3. Our team has established the "Tiaoshen Anti-cancer" theory, conducted a

series of studies on ovarian cancer-related insomnia, and preliminarily confirmed the clinical advantages of the Tiaoshen Anti-cancer regimen.

Our team has long focused on research in the field of psycho-oncology comorbidities, explored the value of "Shen" (mind/spirit) in cancer prevention and treatment, proposed the pathogenesis of tumor formation as "disharmony of Form, Qi, and Spirit," advocated establishing a "Tiaoshen Anti-cancer" research system, and developed a combination of pharmacological and non-pharmacological "Eight Methods of Tiaoshen Anti-cancer" (calming the spirit, adapting to seasons, acupuncture, herbal medicine, Daoyin, Tuina massage, music, psychotherapy). These methods can be selected and combined based on the disease and syndrome. Clinical studies are conducted to screen the clinical efficacy and mechanisms of action of different combinations of pharmacological and non-pharmacological interventions, fully leveraging the patient's active role in cancer treatment and improving the overall efficacy of cancer therapy.

Given that ovarian cancer has the highest mortality rate among gynecological malignancies, and its onset age often coincides with menopause, patients are highly susceptible to psycho-psychological issues such as insomnia, depression, and anxiety. Among these, insomnia is the most clinically significant symptom and a key factor limiting the overall therapeutic efficacy for ovarian cancer. Therefore, our team has focused on this condition. A cross-sectional study investigating the clinical data of 235 postoperative ovarian cancer patients revealed an insomnia incidence rate of 63.83%. Insomnia significantly impacted the incidence and severity of depression and anxiety in patients, while also significantly affecting their quality of life, chemotherapy completion rate, and survival prognosis.

Addressing the postoperative physical constitution of ovarian cancer patients characterized by "vital Qi deficiency, mental restlessness, and latent residual toxin," the applicant proposes the core pathogenesis as "vital Qi deficiency with latent toxin, and heart spirit instability." The treatment principle of "reinforcing vital Qi to treat

cancer, calming the spirit to improve sleep" was established. A specialized formula for cancer-related insomnia, named "Tiaoshen Anti-cancer Formula," was developed by combining the classic formula Suanzaoren Tang with modern pharmacological research findings and was granted a national invention patent (ZL202210718678.8). The formula consists of Suanzaoren (Ziziphi Spinosae Semen), Chonglou (Paridis Rhizoma), Huangqi (Astragali Radix), and Yujin (Curcumae Radix). Suanzaoren acts as the sovereign herb, entering the Heart, Liver, and Gallbladder meridians, nourishing the Heart and Liver to calm the spirit. Huangqi and Chonglou serve as minister herbs; Huangqi primarily enters the Spleen and Lung meridians, strengthening the Spleen and reinforcing vital Qi, supplementing Qi to aid in calming the spirit; Chonglou primarily enters the Liver meridian, detoxifying, resolving masses, and calming fright, assisting in calming the spirit, detoxifying, and fighting cancer. Yujin acts as an adjuvant, entering the Liver, Gallbladder, and Heart meridians, primarily promoting blood circulation, moving Qi, relieving depression, and clearing the heart. To elucidate the mechanism of this formula, our team established a basic research platform for "Tiaoshen Anti-cancer" in collaboration with the National Center for Mental Health - Shanghai Mental Health Center affiliated with Shanghai Jiao Tong University. We found that the active components of the Tiaoshen Anti-cancer formula significantly inhibit ovarian cancer cell proliferation, suppress key glycolytic processes in ovarian cancer cells, and ultimately delay ovarian cancer progression. Additionally, we discovered that components of the Tiaoshen Anti-cancer formula can enhance the expression of the circadian rhythm protein ROR α , thereby improving the circadian rhythm in ovarian cancer and further inhibiting metabolic reprogramming in ovarian cancer.

Subsequently, a multicenter, double-blind, placebo-controlled trial of "Tiaoshen Anti-cancer Formula Granules" for ovarian cancer-related insomnia was conducted. Results showed that the Tiaoshen Anti-cancer formula combined with psychological intervention significantly reduced the peripheral blood CA125 level ($P < 0.05$), improved patients' sleep quality, sleep duration, sleep efficiency, sleep disturbances,

hypnotic medication use, daytime dysfunction scores, and the total PSQI score ($P < 0.05$), and effectively prolonged progression-free survival (PFS) ($P < 0.05$). The Tiaoshen Anti-cancer Formula Granules combined with psychological intervention significantly improved insomnia and related symptoms in ovarian cancer patients and prolonged survival.

Furthermore, our team conducted a prospective clinical study on the effects of the Tiaoshen Anti-cancer formula combined with the "Sleep-Regulating Daoyin Method" on cardiopulmonary endurance and mood in lung cancer patients. The study found that after three months of treatment, this combination significantly improved the scores for the three symptom factors ("difficulty falling asleep," "waking up too early," and "unstable and shallow sleep") in the Symptom Checklist-90 (SCL-90) ($P < 0.01$). Through the above series of clinical explorations, it has been confirmed that the combination of Tiaoshen Anti-cancer Formula, psychotherapy, and Daoyin therapy has clear effects, but its application in different stages of comprehensive ovarian cancer treatment requires further investigation.

In summary, our team focuses on the clinical challenge of psycho-oncology comorbidities, inherits the "Unity of Form and Spirit" theory from the Huangdi Neijing, integrates advancements in oncology and psychology, and has established a comprehensive "Tiaoshen Anti-cancer" research platform to systematically conduct theoretical, clinical, and basic research on cancer-related insomnia.

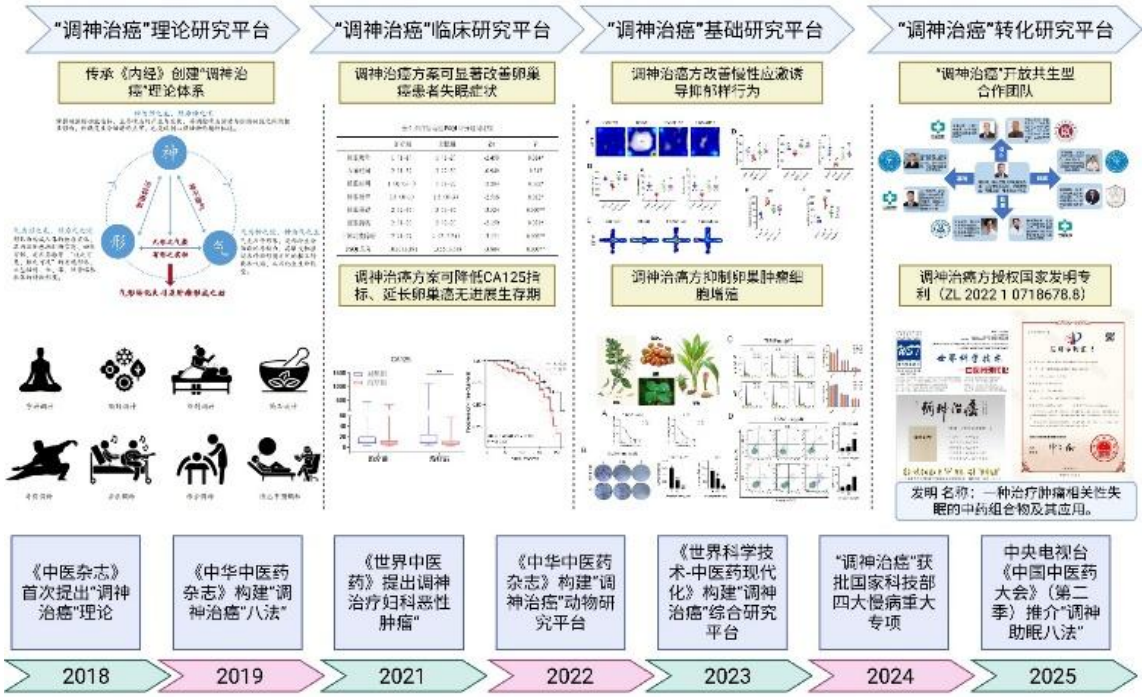

Figure 1-1 Comprehensive Research Platform of Tiaoshen Anti-cancer

II. Research Objectives

1. To clarify the efficacy of the Tiaoshen Anti-cancer regimen combined with Cognitive Behavioral Therapy (CBT-I) in improving ovarian cancer-related insomnia and enhancing quality of life, and to establish an integrated Chinese and Western medicine diagnosis and treatment protocol for ovarian cancer-related insomnia.

2. To evaluate the effect of the Tiaoshen Anti-cancer regimen combined with CBT-I in prolonging the survival of ovarian cancer patients.

3. To construct an artificial intelligence (AI)-driven multimodal predictive model for ovarian cancer-related insomnia to refine the diagnosis and treatment system.

III. Overall Study Design

1. Design Concept of the Study Protocol

A large-sample, prospective, multicenter, two-stage sequential, blinded-assessment

randomized controlled clinical trial design will be employed to evaluate the efficacy and safety of the "Tiaoshen Anti-cancer Formula Granules + CBT-I, followed by the Sleep-Regulating Daoyin Method" for ovarian cancer-related insomnia, as well as its impact on patients' quality of life and survival. This aims to optimize existing treatment protocols and develop an integrated Chinese and Western medicine diagnosis and treatment plan for ovarian cancer-related insomnia to guide clinical practice and improve efficacy.

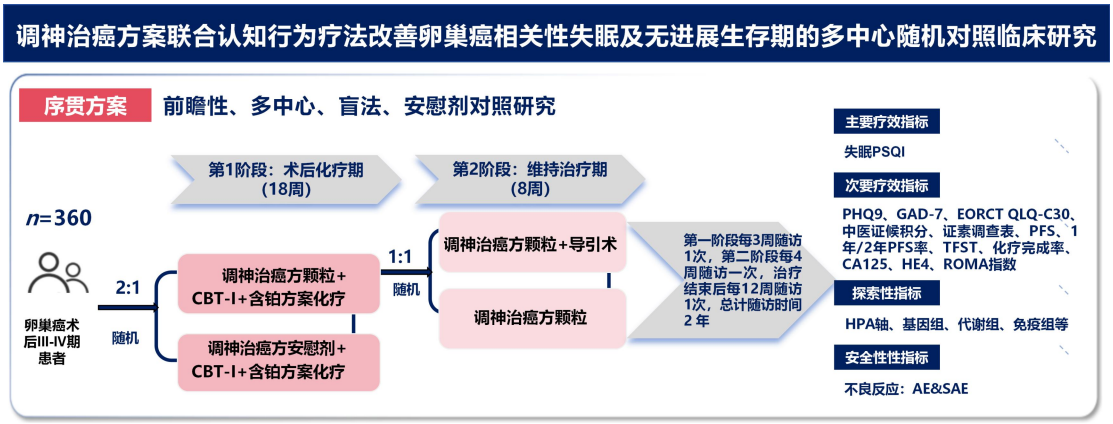

Figure 2-1 Study Protocol

2. Staged Design

Stage 1: Patients will be randomly assigned to two groups in a 2:1 ratio (experimental group: control group). The experimental group will receive "Tiaoshen Anti-cancer Formula Granules + CBT-I + standard first-line platinum-based chemotherapy." The control group will receive "Tiaoshen Anti-cancer Formula Placebo + CBT-I + standard first-line platinum-based chemotherapy." The intervention period is 18 weeks. The primary efficacy outcome is the improvement rate in PSQI score. Secondary outcomes include PHQ-9, GAD-7 scales, TCM syndrome scores, pattern element questionnaires, EORTC QLQ-C30, and sleep diaries. These will evaluate the clinical efficacy of the "Tiaoshen Anti-cancer Formula Granules + CBT-I" regimen combined with standard care in improving ovarian cancer-related insomnia. At the end of this stage, an AI model using multimodal data will generate individual risk and treatment response predictions to guide the random assignment of patients in the experimental

group for the second stage.

Stage 2: Patients who completed Stage 1 in the experimental group will be enrolled. Using a stratified randomization method based on insomnia improvement rate and maintenance chemotherapy regimen, participants will be randomly assigned in a 1:1 ratio to either the experimental group or the control group. The experimental group will receive sequential "Tiaoshen Anti-cancer Formula Granules + Sleep-Regulating Daoyin Method" in addition to standard maintenance treatment. The control group will receive sequential "Tiaoshen Anti-cancer Formula Granules" alone in addition to standard maintenance treatment. The intervention period is 8 weeks. The primary efficacy outcome is the improvement rate in PSQI score. Secondary outcomes include PHQ-9, GAD-7 scales, TCM syndrome scores, pattern element questionnaires, EORTC QLQ-C30, and sleep diaries. This aims to evaluate the clinical efficacy of the "Tiaoshen Anti-cancer Formula Granules + CBT-I, followed by Sleep-Regulating Daoyin Method" combined with standard maintenance therapy in improving ovarian cancer-related insomnia. An AI self-assessment SOP tool will continuously collect symptom data during the intervention period to dynamically adjust the intensity of the Daoyin exercises. Subsequently, a 2-year follow-up will be conducted. Objective indicators such as imaging examinations and tumor marker tests will be used to monitor PFS, 1-year/2-year PFS rates, and time to first subsequent therapy (TFST), to assess the long-term efficacy of the regimen on prognosis. Follow-up data will be continuously fed back to the AI platform to refine the predictive model and generate reports on long-term prognosis and recurrence risk to support individualized long-term management.

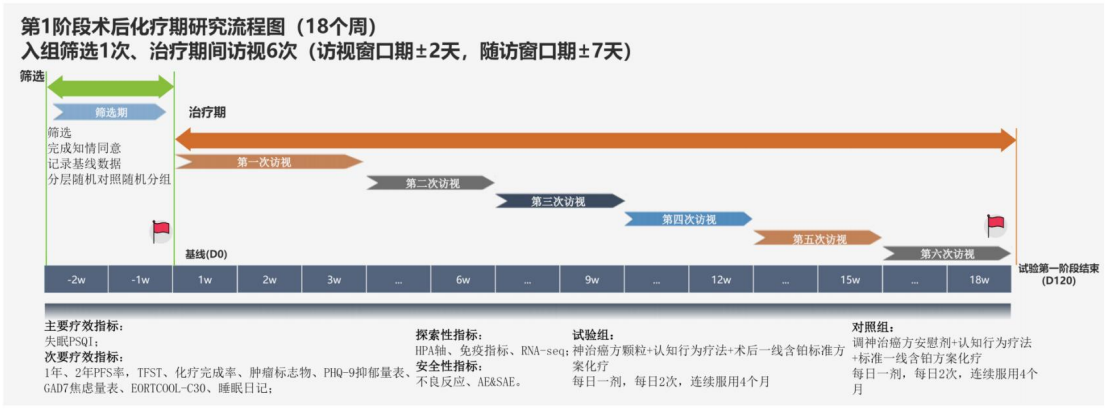

Figure 2-2 Flowchart of Stage 1

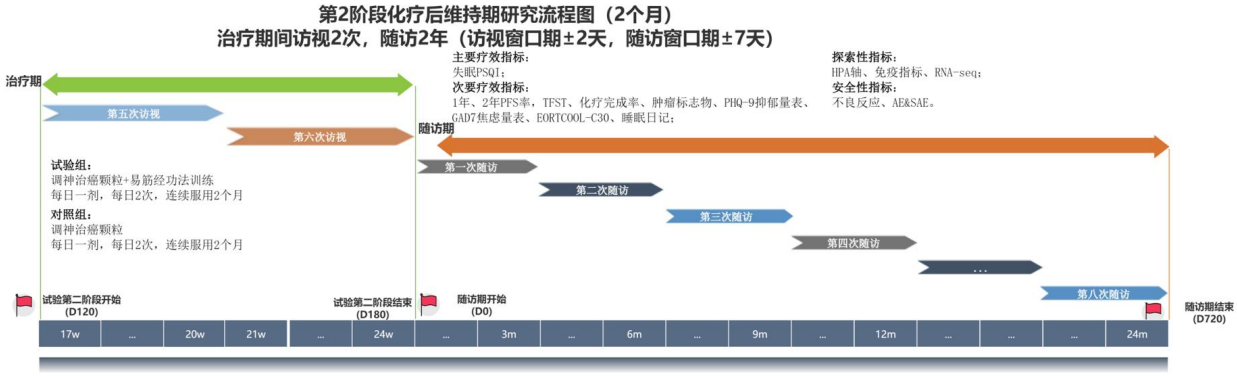

Figure 2-3 Flowchart of Stage 2

3. Randomization

Randomization will be performed by a biostatistician not involved in the data management or statistical analysis of this trial using SPSS version 27.0 to generate the randomization schedule. Stage 1 will employ block randomization with a 2:1 allocation ratio (experimental group: control group) to generate random codes. Stage 2 will use randomized blocks with a 1:1 allocation ratio for patients from the experimental group who completed the study medication, generating random codes. Key information such as the chosen block length and random seed parameters will be kept confidential and sealed in the blind code.

4. Blinding Design

Stage 1: Double-blind design.

Stage 2: Open-label trial with blinded assessors.

4.1 Coding and Management of the Blind Code

After coding, the coder from the statistical unit will transfer the sealed blind code to the lead clinical research unit. The blind code includes two levels of confidential information based on the randomization number:

- **Level 1 Blind Code:** Corresponding group assignment for each case number (e.g., Group A or Group B).
- **Level 2 Blind Code:** Actual treatment corresponding to each group (e.g., experimental group or control group).

The two levels of blind code will be sealed separately, each in duplicate. One copy will be stored at the lead clinical trial site, and the other copy will be stored at an independent quality control department (e.g., the sponsor's quality control office or a third-party institution), with strict security measures.

4.2 Drug Coding and Packaging

Drug coding and distribution packaging will be performed jointly by statisticians not directly involved in this clinical trial and personnel from the sponsor not involved in the trial. Based on the overall stratified block randomization scheme and the drug coding plan, the investigational product and comparator will be assigned unique drug package numbers and drug coding codes, which will be recorded (or affixed) on the drug labels. Packaging will ensure that the investigational product and comparator are completely identical in appearance, characteristics, odor, and packaging during the double-blind phase of Stage 1.

4.3 Blind Code Letters

An individual blind code letter will be prepared for each randomization number. The letter will contain critical information such as the group assignment (A/B) for that

subject and the treatment details (investigational product/comparator) needed in case of emergency unblinding. These letters will also be sealed and stored as required at designated locations (e.g., the research center pharmacy or the lead unit). They will only be opened by authorized personnel according to procedures in emergency situations where unblinding is necessary, such as a Serious Adverse Event (SAE).

4.4 Blinding Design (Staged)

Stage 1: Double-blind design. In this stage, subjects, investigators (including those involved in efficacy and safety assessments), other personnel directly involved in trial implementation and management at the research center, the sponsor's Clinical Research Associate (CRA), and data management personnel will all remain blinded to the subjects' specific group assignment (A/B) and the corresponding treatment (experimental/control).

Stage 2: Open-label trial with blinded assessors. In this stage, subjects, investigators, and relevant management personnel may be informed of the subjects' Stage 1 group allocation information (i.e., experimental/control) and will know the subjects' Stage 2 group allocation (i.e., experimental/control) according to the study protocol requirements.

4.5 Emergency Letters and Emergency Unblinding

Emergency Letter: Each coded investigational product will have a corresponding emergency letter. The emergency letter contains a note indicating the product corresponding to that code, to be used for unblinding in emergencies. The emergency letter will be sealed and distributed to each clinical trial center with the corresponding coded investigational product. It will be stored by the center and must not be opened unless necessary. In emergency situations (e.g., SAE) or when a subject's condition requires knowing the treatment received for resuscitation, a researcher may open it. Emergency letters are for emergency unblinding, strictly authorized, and can only be

opened by the principal investigator at each center. The operation will be documented, including the signatory's name, date, and reason for opening.

In an emergency, if the investigator deems that knowing the subject's assigned medication is beneficial for managing an adverse event, unblinding may be performed. The investigator must perform the unblinding, and the reason, time, and location should be recorded in detail with a signature. Within 24 hours of unblinding, the lead clinical trial unit, Clinical Research Associate (CRA), and relevant statistical personnel must be notified, and the reason for unblinding must be explained. Once an emergency letter is opened, that subject will withdraw from the trial and be considered a dropout. The investigator will record the reason for withdrawal in the Case Report Form (CRF). All emergency letters will be collected along with the CRFs after the trial for blinded review.

4.6 Unblinding Procedures

A two-stage unblinding method will be used. After all CRFs are entered into the database and following queries, verification, and blinded review, the data will be locked. The staff responsible for storing the blind code will perform the first unblinding (i.e., clarifying groups A and B). The information will be provided to the biostatistician for entry into the computer and linkage with the data file for statistical analysis. After the statistical analysis is completed, the second unblinding will be performed to clarify the experimental and control groups.

5. Sample Size Estimation

A large-sample, prospective, multicenter, two-stage sequential, blinded-assessment, superiority randomized controlled trial will be conducted to evaluate the intervention of "Tiaoshen Anti-cancer Formula Granules + CBT-I, followed by Sleep-Regulating Daoyin Method" on ovarian cancer-related insomnia and survival prognosis. The allocation ratio is 2:1 (experimental group: control group). Preliminary clinical studies indicated an improvement rate in PSQI score of 70% in the experimental group

receiving Tiaoshen Anti-cancer Formula Granules combined with CBT-I-based psychological intervention and platinum-based standard chemotherapy (Lu Xinyi, Theoretical discussion and clinical study of Tiaoshen Anti-cancer Formula in treating ovarian cancer-related insomnia [D], Shanghai: Shanghai University of Traditional Chinese Medicine, 2025). The control group receiving placebo combined with CBT-I-based psychological intervention and platinum-based standard chemotherapy is estimated to have a PSQI improvement rate of 50%. The superiority margin (Δ) is 8%, α = 0.025 (one-sided superiority test), β = 0.20, power (1- β) = 80%. The sample size was calculated using the following formula, where p1 = 70%, p2 = 50%, α = 0.025, β = 0.80, Δ = 8%. The calculation yielded n1 = 182, therefore n2 = 91.

$$n_1 = \frac{(z_{1-\alpha} + z_{1-\beta})^2 \times (p_1(1-p_1) + \frac{1}{2}p_2(1-p_2))}{(p_1 - p_2 - \Delta)^2}$$

$$n_2 = \frac{n_1}{2}$$

Based on the above calculation, accounting for a 10% dropout rate, the experimental group requires 200 participants, and the control group requires 100 participants, totaling 300. Considering the stratification factors "ovarian cancer stage" and "multiple centers," the sample size will be increased by 10%. Therefore, this study will recruit at least 360 patients, with 240 in the experimental group and 120 in the control group.

References from the NCCN Guidelines for Cancer Survivorship: Sleep Disorders (2025 V1.0): Johnson JA, Rash JA, Campbell TS, et al. A systematic review and meta-analysis of randomized controlled trials of cognitive behavior therapy for insomnia (CBT-I) in cancer survivors. Sleep Med Rev 2016;27:20-28.

6. Subject Compliance

- Investigators will diligently implement informed consent to ensure subjects fully understand the trial requirements and cooperate. The sponsor will provide the investigational product and cover laboratory examination costs free of charge.

- Medication counting will be used to monitor subject compliance.

  Formula: Compliance (%) = (Actual medication intake / Prescribed medication intake) × 100%

  Compliance between 80% and 120% is considered good; less than 80% or more than 120% is considered poor.

- Investigators will require subjects to bring all medications they are using during follow-up visits to check for concomitant medications and record them in the CRF. Enhanced follow-up will be provided for patients with poor efficacy or irregular medication intake.

IV. Diagnostic Criteria

1. Ovarian Cancer Pathology and Staging

Reference will be made to the International Federation of Gynecology and Obstetrics (FIGO) "Guidelines for Staging of Gynecological Malignancies" and the ESMO 2023 guidelines. Pathological examination will be performed on diagnostic biopsy samples or intraoperative tumor samples by a pathologist. If sufficient tumor samples cannot be obtained, pathological examination of ascites or pleural effusion (if present and safely accessible) will be performed to complete the diagnosis and staging, confirming the disease as epithelial ovarian cancer, FIGO stage III-IV.

2. Ovarian Cancer-Related Insomnia

Reference will be made to the diagnostic criteria for insomnia in the International Statistical Classification of Diseases and Related Health Problems, 10th Revision

(ICD-10). The diagnostic criteria for cancer-related insomnia are: difficulty falling asleep, difficulty maintaining sleep (nocturnal awakenings ≥ 2 times), early awakening with inability to return to sleep, occurring ≥ 3 times per week and persisting for ≥ 1 month.

V. Selection of Subjects

1. Inclusion Criteria

- Patients aged 18 to 80 years.
- Performance Status (PS) score 0-2.
- Histopathologically or cytologically confirmed primary epithelial ovarian cancer, postoperative FIGO stage III-IV, scheduled for standard postoperative first-line platinum-based chemotherapy.
- Have undergone ovarian cancer debulking surgery, are in a stable phase at enrollment (no active infection, severe liver or kidney impairment, etc.), and are scheduled for standard postoperative first-line platinum-based chemotherapy.
- Meet the diagnostic criteria for ovarian cancer-related insomnia, including symptoms such as difficulty falling asleep, sleep maintenance difficulty (nocturnal awakenings ≥ 2 times), early awakening with inability to return to sleep, occurring ≥ 3 times per week and persisting for ≥ 1 month.
- Possess the ability to understand the scales and undergo CBT-I (e.g., Mini-Mental State Examination [MMSE] ≥ 24 points or education level above primary school).
- Signed informed consent form, voluntary agreement to receive the protocol treatment, and ability to independently complete a sleep diary.

2. Exclusion Criteria

- Prior history of systematic CBT-I (to avoid learning effects).
- History of chronic insomnia or mental illness such as depression prior to ovarian cancer diagnosis, with Patient Health Questionnaire-9 (PHQ-9) score ⩾ 15 or Generalized Anxiety Disorder 7-item (GAD-7) scale score ⩾ 15, and a history of long-term use of sleeping pills or psychotropic medications.
- Pregnant or lactating women; patients with severe diseases of the cardiovascular, cerebrovascular, pulmonary, hepatic, renal, or hematopoietic systems.
- Patients with language disorders.
- Patients with autoimmune diseases, congenital/acquired immune deficiencies, hematological diseases, or long-term use of hormones or immunosuppressants.
- Patients with severe or uncontrollable inflammatory conditions such as active hepatitis B or active tuberculosis (e.g., unstable or non-compensated respiratory, cardiovascular, liver, or kidney infections).
- No history of long-term alcohol dependence.
- Patients with other primary tumors.
- Participation in other clinical trials within the past 3 months.
- Patients with no legal capacity, or medical or ethical reasons that affect study continuation.

3. Criteria for Discontinuation from the Study (Excluded Cases)

- Spontaneous remission of insomnia symptoms or worsening requiring emergency intervention.

- Use of prohibited medications that interfere with insomnia assessment during the trial (e.g., other Chinese herbal decoctions, immunotherapies).

- Poor compliance with the study medication, CBT-I, or Daoyin method after enrollment.

- Collection of data reveals missing or invalid key insomnia data.

- Post-enrollment discovery that the subject does not meet the inclusion criteria.

- No evaluable records after receiving any medication.

Cases meeting the discontinuation criteria will have the reason documented, and their CRF will be retained for reference. They will not be included in the efficacy analysis, but if they received at least one treatment and have at least one safety record, they may be included in the adverse reaction analysis.

4. Criteria for Dropout

- Subject withdraws voluntarily.

- Investigator determines the subject should withdraw.

VI. Treatment Protocol

1. Study Grouping

Both groups will follow a sequential treatment protocol, divided into two stages. The investigational product for all centers will be provided by the lead unit according to blinding requirements and will meet quality standards.

Stage 1:

- Experimental Group: Tiaoshen Anti-cancer Formula Granules + CBT-I + standard

first-line platinum-based chemotherapy, with regular outpatient follow-up.

- Control Group: Tiaoshen Anti-cancer Formula Placebo + CBT-I + standard first-line platinum-based chemotherapy, with regular outpatient follow-up.

Stage 2:

All subjects who completed Stage 1 in the experimental group will be enrolled as study subjects for Stage 2. Based on PSQI scores, subjects who were responders or non-responders in Stage 1 will be evenly randomly assigned to the Stage 2 experimental group or control group according to stratification factors for a randomized clinical study.

- Experimental Group: Standard maintenance therapy + Tiaoshen Anti-cancer Formula Granules + Sleep-Regulating Daoyin Method.

- Control Group: Standard maintenance therapy + Tiaoshen Anti-cancer Formula Granules.

2. Investigational Product

Tiaoshen Anti-cancer Formula Granules: Composition includes raw Huangqi (Astragali Radix) 30g, Chonglou (Paridis Rhizoma) 9g, Suanzaoren (Ziziphi Spinosae Semen) 30g, Yujin (Curcumae Radix) 9g. These will be prepared by Jiangyin Tianjiang Pharmaceutical Co., Ltd., strictly following standardized manufacturing processes for TCM granules.

3. Comparator

Tiaoshen Anti-cancer Formula Simulator (Placebo): The placebo will be prepared containing 5% of the active ingredients of the treatment group, with the same quantity, appearance, and odor as the active drug. It will be provided by Jiangyin Tianjiang Pharmaceutical Co., Ltd.

4. Quality Control of Investigational Product

The preparation of Tiaoshen Anti-cancer Formula Granules will utilize a modern intelligent production line, employing advanced techniques such as dynamic counter-current extraction, membrane separation and purification, and spray drying to maximize the retention of active ingredients. Fingerprint technology will be used for quality control of raw materials and intermediate products. A full-chain quality control system, from raw material sourcing to production process monitoring to finished product testing, will be established to ensure that each batch meets the requirements of the Chinese Pharmacopoeia and internal corporate standards, guaranteeing product uniformity, stability, and safety.


发明专利证书

发明名称：一种治疗肿瘤相关性失眠的中药组合物及其应用

发明人：田建辉,刘海涛,姚嘉良,王盼盼,于盼盼,张龙

专利号：ZL 2022 1 0718678.8

专利申请日：2022年06月23日

专利权人：上海市中医医院

地址：200071 上海市静安区芷江中路274号

授权公告日：2023年04月25日　　授权公告号：CN 115025193 B

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2023年04月25日

第1页(共2页)

其他事项参见续页

Figure 2-4 Patent Certificate of Tiaoshen Anti-cancer Formula

Patent Name: A Traditional Chinese Medicine Composition for Treating Cancer-Related Insomnia and Its Application

Patent No.: ZL202210718678.8

5. Specific Intervention Protocols

5.1 Standard First-Line Platinum-Based Chemotherapy

Patients with postoperative FIGO stage III-IV primary epithelial ovarian cancer will receive standard postoperative first-line chemotherapy regimens according to

international guidelines (CSCO 2025 version), specifically:

- Paclitaxel + Carboplatin: Paclitaxel 175 mg/m² IV on day 1, followed by Carboplatin AUC 5-6 IV on day 1, repeated every 3 weeks for a total of 6 cycles.

- Albumin-bound Paclitaxel + Carboplatin: Albumin-bound paclitaxel 260 mg/m² IV on day 1, followed by Carboplatin AUC 5-6 IV on day 1, repeated every 3 weeks for a total of 6 cycles, then maintenance every 3 weeks for 6 cycles.

- Docetaxel + Carboplatin: Docetaxel 60-75 mg/m² IV on day 1, followed by Carboplatin AUC 5-6 IV on day 1, repeated every 3 weeks for a total of 6 cycles.

For patients with carboplatin allergy or who cannot tolerate myelosuppression, nedaplatin or cisplatin may be considered as alternatives.

5.2 Stage 2 Standard Maintenance Therapy

PARP inhibitors or bevacizumab will be used according to the relevant package inserts and guidelines.

6. Administration of Tiaoshen Anti-cancer Formula Granules and Placebo

Twice daily, one sachet dissolved in water, taken orally half an hour after meals.

7. Specific Implementation of Cognitive Behavioral Therapy (CBT-I)

Referring to the CBT-I protocol for cancer patients developed by Perlis et al. (Perlis ML, et al: Cognitive Behavioral Treatment of Insomnia: A Session-by-Session Guide. New York, NY, Springer, 2005) and Garland (Garland SN, et al: Adapting Cognitive Behavioral Therapy for Insomnia. San Diego, CA, Elsevier, 2022, pp 235-256), the design includes 8 individual sessions once a week, preceded by one clinical assessment to exclude patients unsuitable for CBT-I. Specific content:

- Therapist Initial Interview: Introduce treatment considerations, gather sleep habit information, perform initial case conceptualization for insomnia, adjust treatment expectations and set reasonable goals, determine suitability for follow-up treatment, and instruct on sleep diary completion.

- Session 1 (Week 1, Day 1): A. Introduce principles, effects, and timeline of CBT-I, enhance motivation. B. Understand sleep mechanisms, analyze causes of insomnia, including the role of physical and cognitive hyperarousal, impact of cancer/treatment/comorbidities/medications on sleep, differentiate sleepiness from fatigue, and lifestyle effects on cancer recovery. C. Summarize baseline sleep diary, set sleep restriction plan, relax sleep efficiency criteria to 85%; use sleep compression techniques for patients with high anxiety, multiple comorbidities, or undergoing radiotherapy/chemotherapy. D. Relaxation training: provide guidance on progressive muscle relaxation, imagery, or meditation based on patient preference. E. Homework: implement sleep restriction, record sleep diary, perform relaxation training.

- Session 2 (Week 2, Day 1): A. Review data. B. Assess treatment benefits and adherence, discuss non-adherence issues. C. Adjust sleep plan. D. Sleep hygiene education, including addressing cancer-specific factors affecting nighttime comfort. E. Homework: implement sleep restriction, record sleep diary, perform relaxation training.

- Session 3 (Week 3, Day 1): A. Review data. B. Assess treatment benefits and adherence, discuss non-adherence issues. C. Adjust sleep plan. D. Homework: implement sleep restriction, record sleep diary, perform relaxation training.

- Session 4 (Week 4, Day 1): A. Review data. B. Assess treatment benefits and adherence, discuss non-adherence issues. C. Adjust sleep plan. D. Teach stimulus control methods; use counter-control instead of stimulus control for hospitalized patients, those undergoing active treatment, or those with nighttime mobility

limitations. E. Homework: implement sleep restriction and stimulus control, record sleep diary, perform relaxation training.

- Session 5 (Week 5, Day 1): A. Review data. B. Adjust sleep plan. C. Assess treatment benefits and adherence, discuss factors hindering plan execution. D. Homework: implement sleep restriction and stimulus control, record sleep diary, perform relaxation training.

- Session 6 (Week 6, Day 1): A. Review data. B. Assess treatment benefits and adherence, discuss non-adherence issues. C. Adjust sleep plan. D. Identify and challenge maladaptive sleep beliefs, including fears about insomnia's impact on overall health and cancer recurrence risk. E. Implement "worry time" to address daytime problems; use behavioral activation/energy generation techniques to manage daytime fatigue (optional). F. Homework: implement sleep restriction and stimulus control, record sleep diary, complete dysfunctional thought record, perform relaxation training, behavioral assignments (optional).

- Session 7 (Week 7, Day 1): A. Review data. B. Assess treatment benefits and adherence, discuss non-adherence issues. C. Adjust sleep plan. D. Continue challenging maladaptive sleep beliefs. E. Discuss effectiveness of "worry time" or behavioral activation (optional). F. Homework: implement sleep restriction and stimulus control, record sleep diary, complete dysfunctional thought record, perform relaxation training, behavioral assignments (optional).

- Session 8 (Week 8, Day 1): A. Review data. B. Assess overall treatment benefits, address unresolved issues. C. Discuss relapse prevention strategies.

- Quality Control for CBT-I: The therapist team will consist of clinical psychologists and psychotherapists from the Shanghai Mental Health Center. All will undergo 12 hours of training on CBT-I and the study protocol consistency, followed by group supervision for CBT-I every 4 weeks.

8. Daoyin Method Training

Referring to the "Technical Specifications of the Ancient Yi Jin Jing Twelve-Movement Daoyin Method" 2018 (approved by the China Association of Chinese Medicine) and the "Guidance Technical Standards for Self-Health Management via Traditional Chinese Daoyin" 2025 (Pudong New Area Local Standard), the "Sleep-Regulating Daoyin Method" will be administered sequentially after TCM treatment, 3-5 times per week, 30-50 minutes per session, for 8 consecutive weeks.

- **Specific Content of the Sleep-Regulating Daoyin Method:**

  Action Essentials: Sit with legs and feet extended straight, arms at chest level, interlock fingers, turn palms outward, push forward seven times, then push upward seven times. Keep feet straight, legs straight, push toes inward. Lean upper body forward, hold feet with hands, repeat 21 times. Bend knees, sit naturally, quickly rub hands together to warm the palms, massage the Shenshu (BL23) acupoint fourteen times until the lower back feels warm. Then return to a sitting position, regulate breathing, and relax the body and mind.

- **Quality Control for the Sleep-Regulating Daoyin Method:**

  The tumor rehabilitation Daoyin program will be guided by Professor Yan Weibing and Professor Yan Shiqing, representative inheritors of the national intangible cultural heritage "TCM Diagnosis and Therapy - Ancient Yi Jin Jing Twelve-Movement Daoyin Method." Three qualified Daoyin instructors will be trained. They will randomly train enrolled subjects in the Daoyin method. Inpatients will be led by the instructors daily during hospitalization; after discharge, they will practice at home. Outpatients will primarily practice at home after training. Instructional videos will be provided, and instructors will supervise. Videos and a WeChat group will be used for photo/video check-ins to monitor practice adherence. Researchers will strictly follow the clinical trial protocol and standard operating procedures to ensure quality control and protocol

implementation.

Figure 2-5 Sleep-Regulating Daoyin Method

9. Trial Duration

- Stage 1: Intervention period of 18 weeks.
- Stage 2: Intervention period of 8 weeks.

10. Follow-up Period

During treatment: Follow-up visits will occur monthly during the intervention period for scale assessments and distribution of study medication.

Post-treatment: Scale assessments will be conducted every 12 weeks. The total follow-up period is 2 years. This includes tumor-related follow-up and survival follow-up (tumor-related follow-up: after treatment, patients are advised to continue subsequent maintenance therapy and undergo imaging examinations every 12 weeks to assess tumor progression).

11. Concomitant Medications/Treatment Regulations

The use of medications other than those specified in the protocol is prohibited during the study period. In principle, other sleep-aiding herbal medicines, anti-tumor Chinese

patent medicines, or biological agents such as thymosin are prohibited. Any such use, if it occurs, will be truthfully recorded in the CRF.

12. Criteria for Discontinuation of Study Drug

- If a subject's condition worsens during the treatment period, the study drug should be discontinued. Efficacy evaluation and relevant laboratory tests will be completed to conclude the trial. The subject will be considered an evaluable case for non-response and included in the Per-Protocol Set (PPS).

- Other situations where the investigator deems it inappropriate for the subject to continue using the study drug.

VII. Study Procedures

1. Trial Duration

- Stage 1: Intervention period of 18 weeks.

- Stage 2: Intervention period of 8 weeks.

2. Follow-up Period

During treatment: Follow-up visits will occur monthly during the intervention period for scale assessments and distribution of study medication.

Post-treatment: Scale assessments will be conducted every 12 weeks. The total follow-up period is 2 years. This includes tumor-related follow-up and survival follow-up (tumor-related follow-up: after treatment, patients are advised to continue subsequent maintenance therapy and undergo imaging examinations every 12 weeks to assess tumor progression).

VIII. Efficacy Evaluation

1. Primary Efficacy Outcome

The primary outcome is the improvement rate in PSQI score. ActiGraph wGT3X-BT wireless sleep monitors will also be used to assess sleep quality, including sleep onset latency, total sleep time, number of awakenings, and total sleep duration.

2. Secondary Efficacy Outcomes

2.1 Survival Outcome Evaluation

(1) 1-year, 2-year survival, TFST: PFS, 1-year/2-year PFS rates, and time to first subsequent therapy (TFST) will be assessed through regular imaging evaluations from the time of randomization.

A. 1-year PFS rate: Defined as the percentage of patients who have not experienced disease progression or death at 1 year after treatment initiation among all enrolled patients.

Formula: (Number of patients progression-free at 1 year / Total evaluable patients) × 100%

B. 2-year PFS rate: Defined as the percentage of patients who have not experienced disease progression or death at 2 years after treatment initiation among all enrolled patients.

Formula: (Number of patients progression-free at 2 years / Total evaluable patients) × 100%

C. TFST: Defined as the time from randomization to the start of the next new treatment or death.

Formula: $TFST = T_{next\_treatment} - T_{current\_end}$

$T_{current\_end}$: Permanent discontinuation date of current treatment (e.g., last dose date/date of doctor-confirmed discontinuation).

$T_{next\_treatment}$: First administration date of next-line anti-tumor therapy.

(2) Chemotherapy Completion Rate: Treatment completeness will be recorded as the number of chemotherapy cycles completed and reasons for discontinuation. Standard postoperative treatment for ovarian cancer is 6-8 cycles. Completing $\geqslant$ 75% of the planned cycles is considered basically acceptable.

(3) Tumor Markers: Such as CA125, HE4, ROMA index, etc.

2.2 Quality of Life Evaluation

- Comprehensive Evaluation of Patient Depression and Anxiety: PHQ-9 and GAD-7 scales will be assessed at weeks 0, 3, 6, 9, 12, 15, 18, 22, and 26.

- Quality of Life Evaluation: EORTC QLQ-C30, TCM syndrome scores, and pattern element questionnaires will be regularly assessed at weeks 0, 6, 12, 18, 22, and 26. Pattern element questionnaire: Based on the pattern element differentiation method, referencing Zhu Wenfeng's "Theory of Pattern Element Differentiation" (Zhu Wenfeng. Theory of Pattern Element Differentiation. Beijing: People's Medical Publishing House, 2008).

- Sleep Diary: Patients will be instructed to record sleep diaries during the treatment period, documenting basic sleep data such as usual bedtime, sleep onset time, number and timing of nighttime awakenings, morning wake-up time, get-up time, and perceived speed of insomnia improvement.

2.3 Exploratory Outcomes

- Exploration of Effective Targets and Mechanisms of the Tiaoshen Anti-cancer Regimen: Based on follow-up efficacy pre- and post-treatment, 30 patients each

from the treatment and control groups with good and poor treatment responses will be selected. Samples of tumor tissue, peritumoral tissue, and normal tissue will be analyzed using single-cell sequencing, liquid chromatography-mass spectrometry, RNA-seq, and whole-genome NGS to identify biological characteristics (e.g., genomic, metabolomic, immunologic profiles) of the effective population and to elucidate potential targets of the Tiaoshen Anti-cancer Formula Granules.

- AI-Based Big Data Efficacy Prediction Model: Clinical information, liver and kidney function, blood routine, coagulation function, tumor markers, immune markers, and cytokines will be collected. Blood samples will be collected pre- and post-treatment to test relevant indicators (e.g., hypothalamic-pituitary-adrenal (HPA) axis function, assessed by measuring plasma cortisol, adrenocorticotropic hormone, and urinary free cortisol pre- and post-treatment).

IX. Safety Evaluation

1. Safety Observation Indicators

Adverse events (AEs) and serious adverse events (SAEs) will be evaluated according to CTCAE v5.0. Patient adverse reactions during the study will be assessed and truthfully recorded in the CRF.

2. Adverse Reaction Monitoring and Risk Analysis

- Safety Background Information Related to the Investigational Product:

Based on preclinical studies, clinical trial data, and formula composition, changes in the hematopoietic system, digestive system, and urinary system, such as red blood cell count, hemoglobin levels, serum creatinine, blood urea nitrogen, and liver function, should be closely monitored during the trial.

- Observation and Recording of Adverse Events: Observation and Recording: Investigators should carefully observe any adverse events occurring during the clinical study. Subjects should be asked to truthfully report changes in their condition after taking medication, avoiding leading questions. While observing efficacy, attention should be paid to adverse events or unexpected toxic side effects (including symptoms, signs, and laboratory abnormalities). Regardless of whether the AE is related to the study drug, it must be recorded in detail in the CRF, including the time of occurrence, symptoms, signs, severity, duration, laboratory indicators, management measures, course of action, outcome, follow-up time, etc. Concomitant medication use should also be recorded to facilitate analysis of the relationship between the AE and the study drug. Records should be signed and dated.

- Subject Medical Management: When AEs are detected, investigators may take necessary management measures based on the severity, such as dose adjustment or temporary interruption of the drug, and decide whether to terminate the trial. If a serious adverse event occurs, the participating trial site must immediately take necessary measures to ensure subject safety.

3. Severity Assessment

Mild: Mild discomfort, tolerable by the subject without affecting treatment, no special treatment required, no impact on subject recovery.

Moderate: Moderate discomfort, difficult for the subject to tolerate, requires special treatment, directly impacts subject recovery.

Severe: Severe discomfort, life-threatening, lethal or disabling, requires immediate emergency management.

4. Causality Assessment:

Indicators for Causality Assessment of Adverse Events:

- Reasonable temporal relationship between study drug administration and the occurrence of the suspected adverse reaction.
- Whether the suspected adverse reaction matches the known adverse reaction profile of the drug.
- Whether the suspected adverse reaction can be explained by concomitant medication, the patient's clinical condition, or other therapies.
- Whether the suspected adverse reaction disappears or lessens upon drug discontinuation or dose reduction.
- Whether the same reaction reappears upon re-exposure to the drug.

Causality Judgment Criteria: Determine based on the order of the above five indicators. (Table not reproduced for text format, but criteria include categories like "Definitely Related," "Probably Related," "Uncertain," "Probably Unrelated," "Definitely Unrelated").

The incidence of adverse reactions will be calculated using the total number of cases classified as (Definitely Related + Probably Related + Uncertain) as the numerator and all enrolled cases eligible for adverse reaction evaluation as the denominator.

X. Statistical Analysis

1. Statistical Analysis, Description, and Inference

R version 4.4.2 will be used.

- Quantitative data: Normality will be assessed using the Shapiro-Wilk test ($n \leqslant 50$) or Kolmogorov-Smirnov test ($n > 50$). Data following a normal distribution

will be expressed as mean ± standard deviation (Mean±SD). Group comparisons will be performed using the independent samples t-test (if variances are equal) or Welch's corrected t-test (if variances are unequal). Non-normally distributed data will be expressed as median (interquartile range) [M(Q1, Q3)], and group comparisons will be performed using the Mann-Whitney U test (for two groups) or Kruskal-Wallis H test (for multiple groups).

- Qualitative data: Expressed as counts (n) and percentages (%). For binary variables, the chi-square test (χ^2) will be used (Fisher's exact test if expected frequency ≤ 5). For ordinal categorical variables, the Wilcoxon rank-sum test (for two groups) or Kruskal-Wallis H test (for multiple groups) will be used.

- Within-group pre-post comparisons: Paired t-test for normally distributed differences; Wilcoxon signed-rank test for non-normally distributed differences.

- Correlation analysis: Pearson correlation (r) for bivariate normally distributed data; Spearman's rank correlation (ρ) for non-normally distributed or ordinal data.

- All tests will be two-sided, with $P < 0.05$ considered statistically significant.

- Survival data analysis: Progression-free survival (PFS) will be estimated using the Kaplan-Meier method. Differences between groups will be assessed using the log-rank test, and survival curves will be visualized. For univariate analysis of factors affecting PFS, the Kaplan-Meier method with log-rank test will be used for categorical variables. Continuous variables will also be analyzed univariately. Potential prognostic factors with $P < 0.1$ in univariate analysis (combined with clinical significance) will be entered into a stepwise Cox regression model to construct a multivariate model and identify independent prognostic indicators. The test standard is two-sided, with $P < 0.05$ considered significant. Survival curves will be reported with 95% confidence intervals (CI).

2. Handling of Missing Data

First, efforts will be made to minimize missing data during trial design and implementation. For missing data that occur, the handling method will primarily depend on the missing data mechanism. For large samples with Missing at Random (MAR), methods such as Expectation-Maximization (EM) or Multiple Imputation will be used under the guidance of a biostatistician. For Missing Not at Random (MNAR), Last Observation Carried Forward (LOCF) will be used. Additionally, if missing data are imputed in the analysis, analyses will be performed separately on the imputed dataset and the dataset with cases having missing data deleted. If the results differ significantly, possible reasons will be investigated to determine which result is more credible, or both results may be reported.

3. Handling of Outliers

First, decisions regarding outliers should not be made simply before understanding the cause, especially when there are few data points. For identifying univariate outliers: if the data are normally distributed, the PauTa criterion can be followed; if a variable's values are within X ± 3S, it indicates no univariate outliers. If the data are not normally distributed, the Q-test can be used to identify univariate outliers. For multivariate outliers, methods such as standardized residual analysis will be used. For confirmed outliers, two approaches can be taken. If a data entry error is confirmed and cannot be corrected, the data point can be directly deleted. If there is no obvious logical error, analyses will be performed both including and excluding the outlier. If the results are not contradictory, the outlier will be retained. If the results are contradictory and deletion is necessary, a satisfactory explanation from both medical and statistical perspectives must be provided.

XI. Potential Risks and Mitigation Measures

1. Adverse Event Reporting and Management

- **Reporting Method:** Any adverse event, including subjective patient discomfort or laboratory abnormalities, must be taken seriously, carefully analyzed, and measures taken immediately to ensure subject safety.

- **Handling Procedure:** Details will be recorded in the CRF. Depending on the situation, follow-up assessments will be conducted within 24 hours, 7 days, and 14 days. The duration, outcome, and resolution will be recorded.

- **Serious Adverse Event Handling:** Any SAE occurring during the trial must be immediately reported to the lead unit or the lead site's Medical Ethics Committee, completing the "Serious Adverse Event Report Form." If it is a serious adverse reaction, it must also be reported to the National Medical Products Administration within 24 hours. Contact numbers and persons listed in the CRF should be notified.

- **Handling Measures:** In emergencies, the principal investigator at the site may open the corresponding emergency letter (with two witnesses present and documentation). Appropriate management will be implemented based on the revealed drug and symptoms. The outcome will be reported to the clinical monitor. The researcher will record the reason for unblinding, date, management, outcome, and sign the CRF.

2. Follow-up of Unresolved Adverse Events

All adverse events will be followed up until they are properly resolved or the condition stabilizes. Follow-up methods (inpatient, outpatient, home visit, phone, correspondence) may be chosen based on the type and severity of the adverse event.

XII. Quality Control Measures

Standard Operating Procedures (SOPs) will be implemented at the lead unit and each participating center to ensure the quality control and assurance system for the clinical

trial. Corresponding SOPs for this trial will be established to ensure trial quality. All observations and findings in the clinical trial must be verified to ensure data reliability and that conclusions are derived from original data. Quality control will be applied at every stage of data processing to ensure all data are reliable and correctly processed.

1. Investigator Training

Before the trial begins, the monitor, in collaboration with the principal investigator at each site, will conduct training on the study protocol to ensure investigators understand the nature, effects, efficacy, and safety of the investigational product (including relevant pre-clinical data), as well as any new information discovered during the trial.

1.1 CBT-I Therapist Training

Combining theory and practice. Theoretical courses include: sleep science fundamentals, CBT-I technical principles, intervention strategies for special populations (elderly/patients with comorbidities). Practical training includes: simulated therapy (practicing core techniques with standardized patients [SPs]), real cases (managing $\geqslant$ 2 patients under supervision, submitting complete session records), and group supervision (monthly group discussions on technical challenges and ethical issues).

1.2 CBT-I Therapist Quality Control

During training, 10% of course recordings will be randomly selected for third-party review. Post-training, the effectiveness of real patient outcomes (e.g., PSQI improvement rate $\geqslant$ 50%) for the trainees will be assessed.

1.3 CBT-I Therapist Supervision

A supervision team will be established, composed of individuals holding a CBT-I

Registered Therapist certificate for ⩾ 5 years, having treated ⩾ 200 insomnia cases, and having passed supervisor training. Therapists will submit treatment recordings and session notes in advance. Core supervision content includes: technical operation review (checking accuracy of sleep diary analysis, consistency in implementing stimulus control), case conceptualization feedback (evaluating whether the therapist's analysis of the patient's insomnia mechanisms, such as hyperarousal and identification of maladaptive beliefs, is appropriate), and ethics and safety review (verifying informed consent signing, safety plans for high-risk patients).

2. Ensuring Consistency Across Multiple Centers

Establish a multi-center synchronization mechanism: Protocol amendments or drug safety updates will be pushed to all centers via an e-learning platform (e.g., MedSci Academy) within 24 hours; researchers must sign acknowledgment of receipt. Quarterly online quality control meetings will be held to review the consistency of AE record completion across centers (using blockchain-verified templates). Standardize blinding operation training: training requires passing a two-stage assessment: a theoretical exam (question bank provided by the lead unit, passing score ⩾ 90%) and cross-center practical assessment (with quality control staff from other centers verifying operational standardization via video).

3. Clinical Trial Monitoring

Monitors appointed by the lead unit will conduct regular on-site monitoring visits to ensure strict adherence to the study protocol and to verify that source data matches the CRF content.

4. Clinical Trial Auditing

The lead unit may commission auditors to conduct a systematic review of the clinical trial to determine whether execution complies with the protocol and whether data reported by participating sites match medical records or other source documents.

Audits will be performed by personnel not directly involved in the trial.

XIII. Ethical Considerations

The clinical trial must be conducted in accordance with the principles of the Declaration of Helsinki (2024 version) and the ethical, moral, and scientific principles stipulated in the Chinese GCP (2003 version). The trial protocol will be implemented only after approval by the Ethics Committee of the lead clinical research unit.

Before enrolling a patient, the investigator is responsible for providing a complete and comprehensive explanation of the study's purpose, procedures, and potential risks in writing to the patient or their legal representative. Patients must be informed of their right to withdraw from the study at any time. Before enrollment, each patient must be given a written informed consent form. The investigator is responsible for obtaining informed consent before each patient enters the study, and the signed consent form will be kept as part of the clinical trial documentation.

XIV. Publication and Data Sharing

The lead study unit has the right to publish or present any results of this trial at academic conferences. The lead unit may seek comments and input from the investigators before publishing or presenting such results.

Investigators have the right to publish or present the results of this clinical trial after its completion, but such publication or presentation requires written permission from the lead unit. The lead clinical trial unit has the right to publish the final clinical trial summary report in a paper. Investigators at each trial site have the right to authorship, but publication also requires written consent from the lead unit.

Statistical Analysis Plan (Summary)

(Note: While a detailed separate SAP document is typically required, the key

statistical elements are integrated within Section X above. Key components include:)

- Analysis Populations: Full Analysis Set (FAS), Per-Protocol Set (PPS), Safety Set (SS).

- Primary Analysis: Comparison of PSQI improvement rates between groups in Stage 1 (and possibly Stage 2) using a chi-square test or logistic regression adjusting for stratification factors. Superiority testing will be performed.

- Secondary Analysis:

① Continuous outcomes (e.g., PSQI score change, scale scores) will be analyzed using ANCOVA or mixed models for repeated measures (MMRM).

② Time-to-event outcomes (PFS, TFST) will be analyzed using Kaplan-Meier methods and Cox proportional hazards models.

③ Categorical outcomes will be analyzed using chi-square tests or logistic regression.

- Subgroup Analyses: Exploratory analyses may be performed based on stratification factors (e.g., stage, center, insomnia improvement status in Stage 1).

- Interim Analysis: Not specified in the provided text; none planned unless dictated by safety or futility considerations (requires protocol amendment).

- Handling of Missing Data and Outliers: As detailed in Section X.2 and X.3.

- Software: R version 4.4.2 (or later) will be used.

- Significance Level: Two-sided $\alpha = 0.05$. For the primary superiority test in Stage 1, a one-sided $\alpha = 0.025$ will be used.