Informed Consent Form – Information Page

Dear Patient,

Your doctor has diagnosed you with ovarian cancer-related insomnia.

We invite you to participate in a multicenter randomized controlled clinical study of the Mind-Regulating Cancer Treatment Regimen combined with Cognitive Behavioral Therapy for Insomnia (CBT-I) in improving ovarian cancer-related insomnia and progression-free survival, and to compare its efficacy and safety for psycho-neurological symptom clusters with conventional treatment.

Before you decide whether to participate, please carefully read the following information. It will help you understand the study, why it is being conducted, the procedures and duration, and the potential benefits, risks, and discomforts. You may discuss it with your relatives or friends, or ask your doctor for further explanation.

(1) Research Background and Purpose

Ovarian cancer-related insomnia is a type of cancer-related insomnia (CRI). It refers to insomnia symptoms that occur in ovarian cancer patients either accompanying the cancer or during antitumor treatment, including difficulty falling asleep, light sleep with easy awakening, excessive dreaming, and early morning awakening. Ovarian cancer ranks among the highest in both incidence and mortality among female reproductive system malignancies. It is often diagnosed at an advanced stage, has a high tendency for recurrence and metastasis, and a low 5-year survival rate. Compared to men, women's sleep is more susceptible to the effects of surgery, chemotherapy, and the cancer itself. Therefore, ovarian cancer patients exhibit more prominent mental and psychological stress and symptoms such as insomnia, anxiety, and depression. Insomnia, in turn, adversely affects the occurrence and progression of ovarian cancer, including reduced quality of life and shortened survival. CRI can also affect the effectiveness of ovarian cancer treatment and reduce chemotherapy efficacy. Chronic sleep deprivation can lead to chronic, systemic low-grade inflammation, promote inflammation-to-cancer transformation, and suppress immune function. In summary, as a highly prevalent symptom, CRI runs through the entire course of ovarian cancer diagnosis, treatment, and rehabilitation. Its impact cannot be ignored, highlighting the importance of timely and effective systematic intervention.

Our research team has previously established the "Mind-Regulating Cancer Treatment" platform.

Collaborating with top research teams from Shanghai University of Traditional Chinese Medicine, Shanghai Mental Health Center, and Fudan University Shanghai Cancer Center, we have: (1) proposed "Mind-Regulating Cancer Treatment" as an important therapeutic approach; (2) established a clinical assessment system for cancer-related mental and psychological conditions; (3) established an animal research platform; (4) established a drug research platform; (5) established a comprehensive "Mind-Regulating Cancer Treatment" system.

Based on association rule mining and entropy clustering analysis, the core prescription used by Professor Tian Jianhui for treating gynecological tumors was identified. Among them, the Mind-Regulating Cancer Treatment Formula for tumors complicated by mental and psychological abnormalities has shown significant clinical efficacy. This formula is based on the principles of regulating the mind, supporting vital qi, and fighting cancer. Preliminary clinical observations by our team found that the formula significantly improved insomnia symptoms in ovarian cancer patients. After treatment, the treatment group's scores for sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbances, use of hypnotic medications, daytime dysfunction, and the total PSQI score were significantly lower than those in the control group ($P < 0.05$).

Currently, treatments for ovarian cancer range from surgery, radiotherapy, and chemotherapy to biological immunotherapy and targeted therapy. However, clinical practice often overlooks the role of the patient's mental state throughout the disease course, and the improvement in efficacy is not substantial. This study aims to find a new breakthrough to enhance treatment efficacy for ovarian cancer patients.

(2) Who is Eligible to Participate? Who is Not Suitable?

Inclusion Criteria:

A. Patients aged 18 to 80 years.

B. PS score 0-2.

C. Histopathologically or cytologically confirmed primary epithelial ovarian cancer, postoperative FIGO stage III-IV, scheduled for standard first-line platinum-based chemotherapy.

D. 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.

E. Meet the diagnostic criteria for ovarian cancer-related insomnia: 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.

F. Possess the ability to understand the scales and undergo CBT-I (e.g., MMSE ≥24 or education level above primary school).

G. Signed informed consent form, voluntary agreement to receive the protocol treatment, and ability to independently complete a sleep diary.

Exclusion Criteria:

A. Prior history of systematic CBT-I (to avoid learning effects).

B. History of long-term chronic insomnia or mental illness such as depression prior to ovarian cancer diagnosis, with PHQ-9 score ≥15 or GAD-7 score ≥15, and a history of long-term use of sleeping pills or psychotropic medications.

C. Pregnant or lactating women; patients with severe diseases of the cardiovascular, cerebrovascular, pulmonary, hepatic, renal, or hematopoietic systems.

D. Patients with language disorders.

E. Patients with autoimmune diseases, congenital/acquired immune deficiencies, hematological diseases, or long-term use of hormones or immunosuppressants.

F. 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).

G. No long-term history of alcohol dependence.

H. Patients with other primary tumors.

I. Participation in other clinical trials within the past 3 months.

J. Patients lacking legal capacity, or medical or ethical reasons that affect study continuation.

(3) What Will Be Required if You Participate?

① Before enrollment, you will undergo examinations to determine eligibility. The doctor will inquire about and record your medical history and perform a physical examination.

② If you are eligible, the study will proceed as follows. At the start, a computer-generated randomization code will determine your treatment assignment. The first phase of this study uses a 2:1 randomization ratio:

- Treatment group (2/3 probability): Mind-Regulating Cancer Treatment Formula granules + CBT-I + standard first-line platinum-based chemotherapy
- Control group (1/3 probability): Placebo granules + CBT-I + standard first-line platinum-based chemotherapy

Neither you nor your doctor will know or be able to choose the assignment in advance. The first phase treatment period is 18 weeks.

Administration of granules: Twice daily, one sachet dissolved in warm water, taken half an hour after meals, for 18 weeks.

CBT-I: One session per week for 8 consecutive weeks, completed within the first phase.

Second phase (only for patients originally in the treatment group): After completing the 18-week first phase, patients in the treatment group will undergo a second randomization (1:1 ratio):

- Sequential treatment group (50% probability): Western maintenance therapy + Mind-Regulating Cancer Treatment Formula granules + sleep-regulating Daoyin exercises
- Sequential control group (50% probability): Western maintenance therapy + Mind-Regulating Cancer Treatment Formula granules

The second phase treatment period is 8 weeks.

Sleep-regulating Daoyin exercises: 3-5 times per week, 30-50 minutes per session, for 8 consecutive weeks.

Follow-up visits during treatment: You will need to visit the hospital monthly during the treatment period, truthfully report any changes in your condition, and undergo assessments of immune function, tumor markers, liver and kidney function, complete blood count, neuroendocrine function, and quality of life.

After treatment ends: You will enter a 2-year follow-up period, with visits every 12 weeks.

③ Other requirements: You must attend follow-up visits as scheduled. Your adherence is very important for the doctor to evaluate the treatment's effectiveness. You must take the medication as instructed. At each visit, you must return any unused medication and packaging and bring any other medications you are taking. If you need other treatments during the study, please contact your doctor in advance.

(4) Potential Benefits of Participating

You and society may benefit. Your condition may improve, and this study may help develop a new treatment method for other patients with similar conditions.

Participation is a significant decision that requires careful consideration. You should fully understand the study content, risks, and benefits before making an informed decision.

(5) Potential Adverse Reactions, Risks, Discomforts, and Inconveniences

All medications may have side effects. If you experience any discomfort, new changes in your condition, or any unexpected situations during the study, regardless of whether related to the medication, notify your doctor promptly. He/she will assess the situation and provide medical management.

If an adverse event occurs, a medical expert committee will determine its relationship to the investigational product. The sponsor will cover treatment costs for trial-related injuries and provide corresponding compensation. If you experience an injury due to participation, you will receive compensation in accordance with Chinese laws and regulations.

During the study, you will need to attend follow-up visits on time and undergo physical and laboratory

examinations, which may cause inconvenience.

(6) Related Costs

During your participation, you will receive the Mind-Regulating Cancer Treatment Formula/placebo granules, CBT-I, professional guidance on Daoyin exercises, treatment follow-up, and health guidance from oncologists free of charge. There are no additional special charges. Laboratory tests required by the study protocol (including blood routine, liver and kidney function, etc.) will be covered by the sponsor.

If a trial-related injury occurs, the sponsor will pay you compensation. If you require treatment and examinations for other concurrent illnesses, those will not be covered.

(7) Is Personal Information Kept Confidential?

Your medical records (study records, physical and laboratory examination reports) will be fully stored at the hospital. The doctor will record laboratory results in your outpatient records. Researchers, sponsor representatives, the ethics committee, and drug regulatory authorities will be permitted to access your medical records. Any public reports of the study results will not disclose your personal identity. We will make every effort to protect your privacy within the limits permitted by law.

Your pathological specimens will be stored at the hospital. They may be used again in other future research. You may now declare whether you refuse such use. You may choose:

☐ Agree to the specimen being placed in a biobank and agree to its use for related other research.

☐ Agree to the specimen being placed in a biobank, but only agree to its use for this study.

☐ Do not agree to the specimen being placed in a biobank.

(8) How to Obtain More Information

You may ask any questions about this study at any time. Your doctor will leave his/her phone number so that your questions can be answered.

If any important new information becomes available during the study that may affect your willingness to continue participating, your doctor will notify you promptly.

(9) Voluntary Participation and Withdrawal

Your participation is entirely voluntary. You may refuse to participate or withdraw at any time without affecting your relationship with your doctor or losing any medical care or other benefits. Your doctor or the investigator may discontinue your participation at any time based on your best interests. If you withdraw for any reason, you may be asked about your use of the investigational product. If the doctor deems it necessary, you may also undergo laboratory tests and a physical examination. There are many alternative treatment options available if you do not participate or withdraw early. You do not need to participate in this study to receive treatment for your condition. If you choose to participate, we hope you can complete the entire study process.

(10) What to Do Now

Whether to participate is your decision. You may discuss it with your family or friends before deciding. Before deciding, please ask your doctor as many questions as possible until you fully understand the study. Thank you for reading the above information. If you decide to participate, please inform your doctor, who will make all necessary arrangements.

Please keep this information sheet.

Informed Consent Form – Signature Page

Clinical Study Project Name: A Multicenter Randomized Controlled Trial of the Mind-Regulating Cancer Treatment Regimen Combined with Cognitive Behavioral Therapy for Insomnia in Improving Ovarian Cancer-Related Insomnia and Progression-Free Survival

Lead Unit: Shanghai Municipal Hospital of Traditional Chinese Medicine, Shanghai University of Traditional Chinese Medicine

Participating Units: Fudan University Shanghai Cancer Center, Obstetrics and Gynecology Hospital of Fudan University, Shanghai Changhai Hospital (Naval Medical University), Shanghai Mental Health Center

Ethics Approval No. of Lead Unit: 2025SHL-KY-123-01

Consent Statement

I have read the above introduction to this study and have had the opportunity to discuss it with the doctor and ask questions. All my questions have been answered satisfactorily.

I understand the potential risks and benefits of participating. I am aware that participation is voluntary, and I confirm that I have had sufficient time to consider it and understand that:

- I may consult the doctor for more information at any time.
- I may withdraw from this study at any time without discrimination or retaliation, and my medical treatment and rights will not be affected.

I also understand that if I withdraw prematurely, especially due to the medication, it would be very beneficial for me and the overall study if I inform the doctor about any changes in my condition and complete the corresponding physical examinations and laboratory tests.

If my condition changes and I need any other medication, I will seek the doctor's advice beforehand or truthfully inform the doctor afterward.

I agree that drug regulatory authorities, the ethics committee, or sponsor representatives may access my research data.

I ☐ Agree / ☐ Refuse to allow my medical records and biological specimens (blood, urine, pathological specimens) to be used for research other than this study.

I will receive a copy of this signed and dated Informed Consent Form.

Finally, I have decided to voluntarily participate in this study and will try my best to follow the doctor's instructions.

Subject Signature: _____ Date: _____ (Y/M/D)

Subject Contact Phone Number: _____

Investigator Statement

I confirm that I have explained the details of this trial to the subject, including their rights, potential benefits, and risks, and have provided them with a signed copy of the Informed Consent Form.

Investigator Signature: _____ Date: _____ (Y/M/D)

Investigator Work Phone: _____ Mobile: _____

If you have any questions regarding the ethics of this study, you may contact the Medical Ethics Committee of Shanghai Municipal Hospital of Traditional Chinese Medicine by phone: +86 21 56628310.