Informed Consent Form

Protocol Title: An Exploratory Randomized, Double-blind, Placebo-controlled Study on Compound Ciwujia Granules in the Treatment of Depression (Heart-Spleen Deficiency Syndrome)

Informed Consent Form Version No.: 03, June 3, 2025
Research Institution: Shanghai Mental Health Center
Principal Investigator (Responsible Research Physician): Dr. Liu Lanying

The purpose of this informed consent document is to provide you with relevant information regarding this study. After fully understanding the details, you may decide whether or not to participate. The hospital and investigators are obligated to furnish you with all necessary information related to this clinical trial, address any concerns you may have, and allow you to voluntarily determine your participation. This study has been reviewed and approved by the Institutional Ethics Committee of the research center.

Dear Participant,

Greetings! We are the research team from **Shanghai Mental Health Center**. You are being invited to participate in a clinical study investigating **Compound Ciwujia Granules** for the treatment of **depression (Heart-Spleen Deficiency Syndrome)**.

To fully protect your rights and ensure the smooth progress of this study, **please carefully review the following information before making your decision.**

1. Study Objectives, Duration, and Setting

Depression is a prevalent yet serious mood disorder, characterized by persistent low mood and loss of interest as core symptoms, accompanied by alterations in cognition, behavior, and physiological functions. Unlike transient emotional fluctuations, depression significantly impairs daily life, occupational performance, and interpersonal relationships. Current clinical treatments for depression remain limited in efficacy, often accompanied by adverse effects. A key scientific challenge of this study is whether traditional Chinese medicine (TCM) can enhance the therapeutic effects of existing SSRIs. To address this research gap, the present study aims to investigate the **potential efficacy of Compound Ciwujia Granules** in improving depressive symptoms. The study will take place from June 1, 2025 to May 31, 2026. Participant recruitment and treatment will be conducted at the Shanghai Mental Health Center.

2. Eligibility Criteria for Study Participation

A total of 60 participants will be enrolled in this study. The inclusion criteria are as follows:

(1) Meet the diagnostic criteria for Major Depressive Disorder according to DSM-5 (Diagnostic and Statistical Manual of Mental Disorders, 5th Edition) and the depressive episode criteria of the Mini-International Neuropsychiatric Interview (M.I.N.I.);
(2) Fulfill the diagnostic criteria of Heart-Spleen Deficiency Syndrome in Traditional Chinese Medicine (TCM):
(3) -Primary symptoms: Excessive contemplation, palpitations, shortness of breath, pale complexion。
(4) -Secondary symptoms: Dizziness, fatigue, spontaneous sweating, poor appetite, loose stools.
(5) -Tongue and pulse: Pale and tender tongue with tooth marks, white tongue coating, thready and weak pulse
(6) Score between 8-24 (inclusive) on the 17-item Hamilton Depression Rating Scale (HAMD-17) Chinese version;
(7) Score ≤21 on the Hamilton Anxiety Rating Scale (HAMA);
(8) Outpatients aged 18-65 years (inclusive) of either gender;
(9) Minimum junior high school education with capacity to complete self-assessment scales;
(10) Currently taking one SSRI medication at a stable dose for ≥6 weeks, with a CGI-GI score ≥4;
(11) Voluntary participation with signed informed consent.

3. Study Treatment

This study includes two groups: **Compound Ciwujia Granules** and **placebo**, with 30 participants in each group. The placebo will be manufactured to match the appearance of Compound Ciwujia Granules but will contain no active ingredients. One group will receive Compound Ciwujia Granules and the other group will receive placebo to compare the efficacy (including effectiveness and inferiority) of the two treatments. Participants will be randomly assigned to either group via computer-generated randomization, ensuring an equal chance (50%) of being allocated to each group. Neither the study physicians nor the participants will know which treatment is being administered (double-blind design). This approach ensures objective evaluation of the study outcomes.

4. Study Procedures

If you agree to participate in this study, our research physician will conduct a detailed

discussion with you or your family members to explain the study details. You will be asked to provide basic information, including: Physical health status, Age, Educational background, Family history and Medical history.

Pre-study Screening:
Before formal enrollment, you will undergo necessary examinations and assessments. If you meet all eligibility criteria, you will be officially enrolled and assigned a unique study identification number. A participant file will be established for each subject.

Note: You may be excluded from the study if any requirements are not met. The research physician will explain the specific reasons to you.

Study Timeline & Assessments:
All enrolled participants will receive:

1) **Complimentary health assessments** at:
    - Baseline (before treatment)
    - Week 4 of treatment
    - Week 8 of treatment
    - 1 month post-intervention
2) **8-week medication supply**

Detailed Study Procedures:

(1) Health Status Assessments
Comprehensive evaluations will include:

- **Demographic data** (age, gender, education, etc.)
- **Current mood state**
- Standardized scales:
    ∟ 17-item Hamilton Depression Rating Scale (HAMD-17)
    ∟ TCM Syndrome Differentiation Scale
    ∟ Hamilton Anxiety Scale (HAMA)
    ∟ Pittsburgh Sleep Quality Index (PSQI)
    ∟ Clinical Global Impression-Improvement Scale (CGI-GI)

(2) Physical Examinations

- Vital signs: Height, weight, blood pressure, pulse

- General systemic examination

(3) Blood Tests

- Two venous blood collections (5ml each):
  - Baseline (pre-treatment)
  - Week 8 of treatment
- Laboratory analyses: Routine blood tests, biochemical markers

(4) Urine Tests

- Two urine samples (10ml each):
  - Baseline (pre-treatment)
  - Week 8 of treatment
- Laboratory analyses: Routine urinalysis

(5) Medication Protocol

- Study drug: Compound Ciwujia Granules or matched placebo
- Dosage: 1 packet twice daily (morning and evening)
- Administration: Orally with warm water

(6) Scheduled Visits

- Mandatory clinic visits at:
  - Week 4
  - Week 8
- During visits:
  - Report all symptom changes truthfully
  - Physician will document medical history updates
  - Physical examination will be repeated

(7) Follow-up Requirements

- Strict adherence to scheduled follow-up visits is crucial for:
  - Treatment efficacy evaluation
  - Safety monitoring
- Medication compliance:
  - Record each dose immediately after administration using the "Medication Log Card"
  - Return all unused study drug and packaging at each visit

∟ Bring all concomitant medications (including those for comorbid conditions)

5. Anticipated Circumstances and/or Reasons for Participant Discontinuation, and Related Management

You may be withdrawn from the study under the following circumstances:
(1) Occurrence of study-related injuries or any other reasons warranting discontinuation;
(2) Non-compliance with the study protocol, including failure to complete required tests and questionnaires as instructed.

6. Alternative Treatment Options
You may opt for alternative therapeutic approaches, including:

- **Other antidepressant medications**: These may provide rapid symptomatic relief but carry potential adverse effects (e.g., gastrointestinal disturbances).
- **Traditional Chinese Medicine (TCM) decoctions**: While generally associated with fewer adverse reactions, TCM interventions may require prolonged administration periods, demonstrate slower onset of action, and potentially exhibit suboptimal symptom control.

7. Participant Responsibilities

(1) Provide accurate information regarding your medical history and current health status.
(2) Report any discomfort experienced during the study period to the research physician.
(3) Disclose any recent or current participation in other clinical studies.
(4) Actively cooperate throughout the study process. Promptly communicate any questions or special requests. If unable to participate due to exceptional circumstances, please notify us in advance (Dr. Tian, Mobile: +86 18501659097).
(5) Diligently complete all tests and questionnaires, and adhere to the 8-week treatment intervention.

8. Anticipated Risks and Discomforts

Compound Ciwujia Granules may cause adverse reactions including but not limited to: Allergic reactions, Nausea, Dry mouth, Headache, Diarrhea,

Constipation, Skin rash and Palpitations. Should you experience any discomfort, new symptoms, or unexpected events during treatment - regardless of perceived relationship to the study drug - immediately notify your physician (Dr. Tian, Mobile: +86 18501659097) for clinical evaluation and appropriate medical management.

9. Anticipated Benefits

By participating in this study, you may receive:

- Necessary therapeutic recommendations for your condition
- Valuable contributions to advancing scientific understanding of the disease

10. Restricted Foods and Medications

No dietary restrictions apply during this study.

Throughout the study duration, the following medications/therapies that may interfere with the evaluation of treatment efficacy and safety are strictly prohibited:

(1) **Antidepressants** (beyond current SSRI and study medication):

a) Monoamine oxidase inhibitors (MAOIs)

b) Serotonin-norepinephrine reuptake inhibitors (SNRIs)

c) Any Chinese herbal medicines or proprietary Chinese formulations with antidepressant effects

(2) **Psychotropic medications**:

a) Benzodiazepine sedative-hypnotics

b) All anxiolytics

c) All antipsychotics

d) Mood stabilizers

11. Compensation/Indemnification

- Participation does not entitle you or your family to financial compensation.
- If you experience study-related injuries during the trial period:
  ∟ You will receive complimentary medical treatment
  ∟ Appropriate compensation will be provided
  ∟ All associated costs will be covered by the research grant

12. Anticipated Costs for Participation

All study-related interviews, assessments, and treatments will be provided **free of charge**. The research team assumes full financial responsibility for all study-associated costs.

13. Participant Rights

Voluntary Participation:

(1) Your participation is entirely voluntary,
(2) You may decline to participate or withdraw at any time without penalty,
(3) Withdrawn participants' data will be excluded from study results,
(4) Your medical care and rights will not be affected by participation decisions.

Regulatory Oversight:

Monitors, auditors, Institutional Review Board (IRB) and regulatory authorities may directly access your original medical records to verify trial procedures.

14. Confidentiality

Your privacy will be strictly protected, and all research data will remain confidential. The principal investigator and research staff will utilize your medical information for study purposes, which may include: name, address, contact number, medical history and study visit records to ensure anonymity:

- Your data will be labeled with a unique study ID instead of personal identifiers
- Identifiable information will not be disclosed to non-study personnel without your explicit consent
- All research staff and sponsors are contractually obligated to maintain confidentiality

Data Management:

- Research records will be stored as secured documents accessible only to authorized personnel
- Original data will be archived at the research facility
- De-identified data may be:
  ∟ Stored electronically (password-protected) and/or physically (locked

cabinets)

∟ Analyzed for research purposes

∟ Reviewed by the Ethics Committee and funding agencies to verify study integrity

Publication:
Study results may be disseminated through:

- Academic journals
- Scientific conferences
  Note: All publications will use aggregate data only, with no personal identifiers.

15. Contact Information

You may access information and updates about this study at any time. For questions related to the study, contact Dr. Tian at 18501659097.

For any discomfort, injury, or questions on participant rights during the study, contact the Ethics Committee of Shanghai Mental Health Center at 021-34773308.

Informed Consent Form – Signature Page

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Participant Declarations:

☑ I have carefully read this informed consent form.
☑ I have had the opportunity to ask questions, and all questions have been answered to my satisfaction.
☑ I voluntarily agree to participate in this study and authorize the use of my data for research analysis.
☑ If I meet the study eligibility criteria and choose to participate, the physician will enroll me in the study.
☑ I have been informed of the expected duration of study participation.
☑ I have been informed of all procedures and assessments involved in the study.
☑ I understand the potential risks and benefits associated with study participation.
☑ By signing this consent form, I do not waive any of my legal rights.
☑ I voluntarily sign this informed consent form prior to study enrollment.
☑ I may choose not to participate or withdraw at any time without facing discrimination or retaliation, and my medical care/rights will not be compromised.
☑ The investigator may discontinue my participation if:1) I require alternative treatments, 2) I fail to comply with the study protocol, 3) Study-related injuries occur, 4)Other justified reasons arise.

☑ I will receive a signed copy of this informed consent form.

Participant Section

Full Name (Block Letters): _____
Participant Signature: _____
Contact Information: _____
Date: _____ Year _____ Month _____ Day

Investigator Certification

I have accurately presented this document to the participant, who has read the complete informed consent form and Voluntarily agreed to participate.

Investigator Name (Block Letters): _____
Investigator Signature: _____
Date: _____ Year _____ Month _____ Day