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Study Protocol

(Version number: 2.0 Version date: 2025.08.21)

Project Title: Effect of Transcranial Magnetic Stimulation vs Sham Stimulation Combined With Pinaverium Bromide vs Bifidobacteria in Diarrhea-Predominant Irritable Bowel Syndrome: A 2×2 Factorial Randomized Clinical Trial

Sponsor: The First Affiliated Hospital of Soochow University

Responsible Department: Gastroenterology Department

Principal Investigator: Rui Li

Participating Centers: Xiangcheng People's Hospital of Suzhou, The People's Hospital of Suzhou New District

Investigator Statement and Protocol Signature Page

As the principal investigator of this research project, I hereby commit to adhering to the ethical principles outlined in the National Health Commission's "Ethical Review Measures for Biomedical Research Involving Humans" (2016), the WMA's "Declaration of Helsinki" (2013), the CIOMS's "International Ethical Guidelines for Biomedical Research Involving Human Subjects" (2002), and Good Clinical Practice (GCP). Under the guidance of the Quality Management Standards for Drug Clinical Trials, I will implement the study protocol approved by the Ethics Committee and conduct the research in strict accordance with the requirements of this protocol, ensuring the scientific validity of the study and protecting the health and rights of the subjects.

Name: Rui Li

Signature: 

Date:2025.07.01

Protocol Synopsis

Study objective	(1) To evaluate the alleviating effect of repetitive transcranial magnetic stimulation (rTMS) on chronic visceral pain in patients with diarrhea-predominant irritable bowel syndrome (IBS-D); (2) To assess the interventional effect of pinaverium bromide and bifidobacterium used alone on chronic visceral pain in IBS-D; (3) To analyze potential interactions between the two intervention measures.
Sample size	140
Study population	Patients with diarrhea-predominant irritable bowel syndrome
Study design	Randomized, controlled factorial design study
Inclusion criteria	(1) Age range 18-75 years (either sex) (2) Fulfilling the Rome IV criteria for irritable bowel syndrome diagnosis (3) Bristol stool type 6-7 in >25% and type 1-2 in <25% of bowel movements (4) Patients experienced Bristol stool type 6 or 7 on ≥4 days with mean abdominal pain score ≥3 during the initial 2-week period
Exclusion criteria	(1) Documented organic gastrointestinal pathology; endocrinologic or metabolic diseases with known gastrointestinal motility effects including diabetes mellitus and hyperthyroidism; previous surgical interventions involving abdominal cavity intestinal tract or anal region (2) current use of any medication with documented effects on gastrointestinal motility or secretory function; administration of concurrent therapies or pharmacologic agents capable of confounding treatment efficacy or safety evaluations (3) pregnancy lactation or postpartum status within 12

	months (4) noncompliance with randomized treatment allocation or demonstrated poor adherence tendencies
Intervention	(1) IBS patients receiving rTMS stimulation + pinaverium bromide treatment rTMS stimulation: 1 Hz, 80% MT, 20 min/d, once daily for 2 weeks; Pinaverium bromide: Oral, 3 times daily, 1 tablet/time, for 2 weeks; (2) IBS patients receiving rTMS stimulation + bifidobacterium treatment rTMS stimulation: 1 Hz, 80% MT, 20 min/d, once daily for 2 weeks; Bifidobacterium: Oral, 2 times daily, 4 capsules/time, for 2 weeks; (3) IBS patients receiving sham rTMS + pinaverium bromide treatment Sham rTMS treatment: 0 Hz, 0% MT, 20 min/d, once daily for 2 weeks; Pinaverium bromide: Oral, 3 times daily, 1 tablet/time, for 2 weeks; (4) IBS patients receiving sham rTMS + bifidobacterium treatment Sham rTMS stimulation: 0 Hz, 0% MT, 20 min/d, once daily for 2 weeks; Bifidobacterium: Oral, 2 times daily, 4 capsules/time, for 2 weeks;
Primary endpoint	The primary outcome measure is the proportion of patients achieving a composite response at the end of treatment

	(Week 2), defined as: a reduction of ⩾30% from baseline in the average daily worst abdominal pain score, and a reduction of ⩾50% in the number of days with at least one stool consistency meeting BSFS type 6 or 7 criteria during Week 2. Abdominal pain intensity is assessed using an 11-point NRS scale (0-10) for the last 24 hours daily. Stool consistency is recorded daily by the patient selecting the most representative category according to the BSFS.
Secondary endpoints	1) Anorectal manometry: Record the subject's initial sensation threshold, constant urge sensation threshold, and maximum tolerable volume at baseline (before treatment) and after the end of treatment. 2) IBS Symptom Severity Score (IBS-SSS): Evaluated at 1 week, 2 weeks, and 4 weeks after treatment. 3) IBS Quality of Life (IBS-QoL) score: Evaluated at 1 week, 2 weeks, and 4 weeks after treatment.
Study timeline	2025.07.1-2026.03.30: Recruit 20-25 patients with diarrhea-predominant IBS meeting Rome IV criteria monthly through multiple centers, using standardized screening procedures (including symptom assessment, exclusion checks, and baseline tests), aiming to complete randomization of 140 cases within 12 months.
Statistical analysis	Use Shapiro-Wilk test to assess normality. Parametric t-test, Wilcoxon rank-sum test, or Kruskal-Wallis test will be used to evaluate continuous data between groups as appropriate.

1.Background

Irritable bowel syndrome (IBS) is a clinically common functional gastrointestinal disorder, affecting 10%-25% of the world's population. The prevalence of IBS in China ranges from 5% to 11%[1]. Among patients visiting the gastroenterology specialty outpatient clinic of our hospital, IBS accounts for more than one-third of cases, with diarrhea-predominant IBS (IBS-D) being the most common subtype. Current symptomatic treatments in both Western and traditional Chinese medicine can temporarily alleviate symptoms of intestinal dysmotility. However, these therapies may cause varying degrees of side effects and lack personalized treatment strategies. In Western countries, over 50% of patients turn to complementary and alternative therapies due to insufficient or unstable symptom relief following pharmacological treatment[2].

A substantial body of literature reports that Transcranial Magnetic Stimulation (TMS) can alleviate chronic visceral hypersensitivity. The specific mechanisms include TMS's ability to modulate cortical excitability, improve cerebral blood flow and metabolism, regulate neurotransmitters and gene expression, as well as induce neural plasticity changes[3]. Our preliminary basic research identified the claustrum–anterior cingulate cortex neural circuit as a unique pathway regulating chronic visceral hypersensitivity in IBS animal models. Translating this finding to clinical applications, TMS-based modulation of this circuit has been shown to alleviate chronic visceral hypersensitivity in IBS patients[4]. Building on these initial results, the current study aims to further expand the sample size and conduct a multicenter randomized controlled trial to validate the long-term efficacy and safety of rTMS in IBS patients with chronic visceral pain, thereby providing higher-level evidence for its clinical application. As a non-invasive stimulation technique with a favorable safety profile, TMS demonstrates significant therapeutic advantages in clinical practice[5]. Therefore, through this study, we aim to further investigate the clinical efficacy of TMS in treating chronic visceral pain associated with irritable bowel syndrome.

2. Study Objectives

2.1 Primary Objectives

(1) To evaluate the alleviating effect of repetitive transcranial magnetic stimulation (rTMS) on chronic visceral pain in patients with diarrhea-predominant irritable bowel syndrome (IBS-D); (2) To assess the interventional effect of pinaverium bromide and bifidobacterium used alone on

chronic visceral pain in IBS-D; (3) To analyze potential interactions between the two intervention measures.

3. Rationale

3.1 Preclinical Animal Experiments and Literature Basis

The mechanisms underlying chronic visceral pain in IBS are complex. The ascending transmission of nociceptive signals primarily involves peripheral noxious information being transmitted via primary sensory neurons to the dorsal horn of the spinal cord, where it is integrated and relayed further to the brain. Current mechanistic research on chronic visceral pain in IBS primarily focuses on the peripheral primary sensory neurons and central brain levels[6]. Studies on the central sensitization mechanism of visceral pain include alterations in neuronal excitability in pain-related brain regions, changes in synaptic transmission, and abnormalities in neural circuit function. Our previous collaborative research with Professor Xu Guangyin's team at the Institute of Neuroscience, Soochow University, demonstrated that adverse neonatal stimuli (such as maternal deprivation) lead to increased neuronal excitability in the insular cortex and enhanced function of the claustrum–anterior cingulate cortex (ACC) neural circuit, thereby inducing chronic visceral pain[7]. These findings suggest that the central nervous system plays a critical role in the pathophysiology of chronic visceral pain in IBS. In the first part of our foundational study, using an animal model simulating chronic visceral pain in IBS, we found that the glutamatergic neural circuit between the ACC and medial prefrontal cortex (mPFC) is involved in the development and persistence of chronic visceral pain, indicating that this circuit may be a key mechanism regulating chronic visceral pain in IBS. These results not only reveal the neural circuit mechanisms underlying central sensitization in chronic visceral pain but also provide new evidence for the regulatory role of the central nervous system in the pathophysiology of IBS. Based on this research, the critical role of the central nervous system in IBS-related chronic visceral pain has become increasingly clear, providing a important theoretical foundation for developing treatments targeting the central nervous system.

However, current treatment strategies for chronic visceral pain in IBS predominantly focus on peripheral interventions, such as pharmacological, psychological, and dietary modifications.

Although these approaches can provide temporary symptomatic relief, they are limited by unstable efficacy and significant side effects[8]. Therefore, there is an urgent need to explore treatments that target the central nervous system, offering holistic regulation, greater safety and efficacy, and fewer side effects. Central neuromodulation, as an emerging therapeutic strategy, holds promise for breakthroughs in treating chronic visceral pain in IBS by directly modulating pain-related neural circuits and brain functions. In particular, the rapid advancement of neuromodulation technologies in recent years has attracted widespread attention in the field of chronic pain management. Among these, repetitive transcranial magnetic stimulation (rTMS) has become a research focus due to its non-invasive, painless, and safe profile[9]. rTMS delivers repeated magnetic stimuli via an electromagnetic coil placed on the head, transferring energy to brain tissue to generate electric currents that modulate neuronal excitability and cerebral metabolism, thereby achieving therapeutic effects. Since its introduction, rTMS has been widely used to treat neurological and psychiatric disorders. The 2014 rTMS treatment guidelines indicate[10] that rTMS can be used to treat various conditions, including pathological pain, movement disorders, disorders of consciousness, tinnitus, depression, and anxiety disorders. Previous studies have shown that rTMS can directly excite the thalamus via corticothalamic projections, inhibiting the transmission of sensory information through the spinothalamic tract, thereby alleviating abdominal pain in patients with chronic pancreatitis[11]. However, research on whether rTMS can alleviate chronic visceral pain in IBS patients remains limited[12,13], and the specific mechanisms of rTMS intervention in IBS-related chronic visceral pain are not yet fully understood. Based on our previous findings, the ACC-mPFC glutamatergic neural circuit may play a key role in the development and persistence of chronic visceral pain in IBS[14-17], leading us to a new research question: Could rTMS, by modulating excitability in the mPFC and influencing the ACC-mPFC glutamatergic circuit, become a novel intervention for chronic visceral pain in IBS patients? This question warrants in-depth investigation.

Therefore, this study aims to explore the efficacy of rTMS intervention for chronic visceral pain in IBS, seeking to elucidate the specific mechanisms by which rTMS alleviates chronic visceral pain through modulation of pain-related neural activity (e.g., in the mPFC) and neural network interactions (e.g., the ACC-mPFC circuit). This research will not only provide central evidence

supporting the clinical effects of rTMS for chronic visceral pain in IBS but also establish an experimental foundation for future clinical applications.

3.2 Subject Selection Rationale

This study selects patients who meet the Rome IV diagnostic criteria for irritable bowel syndrome, with Bristol Stool Form Scale types 6-7 accounting for >25% of bowel movements, and hard/lumpy stools (types 1-2) accounting for <25%. Age range is between 18-75 years. During the 2-week run-in period, the patient has at least 4 days with diarrheal stools (Bristol Stool Form Scale type 6 or 7), and an average abdominal pain intensity ≥3 points (based on a 0 to 10 point Numerical Rating Scale [NRS]).

3.3 Endpoint Selection Rationale

The primary outcome measure is the proportion of patients achieving a composite response at the end of treatment (Week 2), defined as: a reduction of ≥30% from baseline in the average daily worst abdominal pain score, AND a reduction of ≥50% in the number of days with at least one stool consistency meeting BSFS type 6 or 7 criteria during Week 2. Abdominal pain intensity is assessed using an 11-point NRS scale (0-10) for the last 24 hours daily. Stool consistency is recorded daily by the patient selecting the most representative category according to the BSFS.

3.4 Risk and Benefit Rationale

This study adopts a strict risk-benefit assessment system. Potential risks mainly include three aspects: rTMS-related risks (10-15% of subjects may experience transient headache or scalp discomfort, seizure risk <0.1%); pinaverium bromide may cause dry mouth and constipation (incidence about 12%); bifidobacterium may cause mild bloating (incidence 8-10%). Main benefits are reflected in: 1) Clinical level: it is expected that 60% of patients in the combination therapy group will achieve a reduction in abdominal pain VAS score of ≥50%, and an increase in quality of life score (IBS-QOL) of ≥20 points; 2) Long-term benefit: the recurrence rate in the combination group at the 3-month follow-up is significantly lower than in the single-drug groups.

4. Sample Size Calculation

We tested the null hypothesis of no difference in composite response rates between groups. Based on previous literature[18-20]and our preliminary trial, assuming a placebo response rate of 23.8%, we expected to double the response rate, assuming a composite response rate for repetitive transcranial magnetic stimulation of 47.61%. At a significance level of $\alpha = 0.05$, 63 patients per group are needed to detect a 23% difference with 80% statistical power. Considering a 10% dropout rate, the final estimated sample size required is 140 patients. [This center will recruit 70 cases, Xiangcheng People's Hospital of Suzhou will recruit 40 cases, and Suzhou New District People's Hospital will recruit 30 cases.

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Tests for Two Proportions

Numeric Results for Testing Two Proportions using the Z-Test with Pooled Variance

Hypotheses: H0: P1 - P2 = 0 vs. H1: P1 - P2 ≠ 0

Target Power	Actual Power*	N1	N2	N	P1	P2	Diff D1	Alpha
0.8	0.80393	63	63	126	0.47619	0.2381	0.2381	0.05

* Power was computed using the normal approximation method.

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Report Definitions

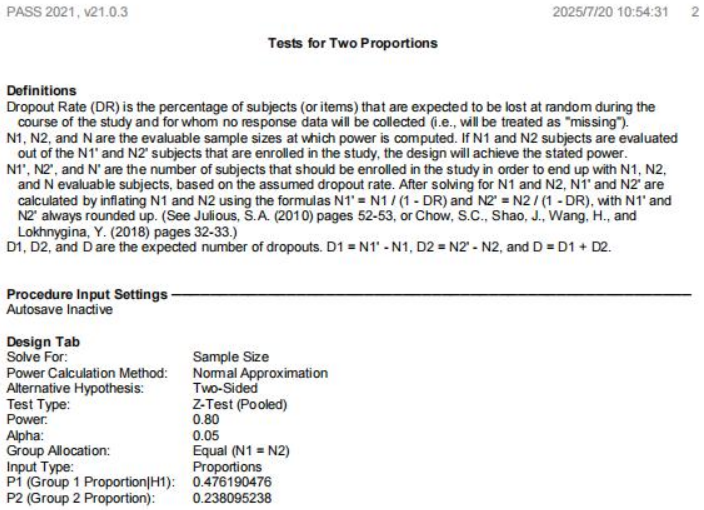
Target Power is the desired power value (or values) entered in the procedure. Power is the probability of rejecting a false null hypothesis.
Actual Power is the power obtained in this scenario. Because N1 and N2 are discrete, this value is often (slightly) larger than the target power.
N1 and N2 are the number of items sampled from each population.
N is the total sample size, N1 + N2.
P1 is the proportion for Group 1 at which power and sample size calculations are made. This is the treatment or experimental group.
P2 is the proportion for Group 2. This is the standard, reference, or control group.
D1 is the difference P1 - P2 assumed for power and sample size calculations.
Alpha is the probability of rejecting a true null hypothesis.

Summary Statements

Group sample sizes of 63 in group 1 and 63 in group 2 achieve 80.393% power to detect a difference between the group proportions of 0.2381. The proportion in group 1 (the treatment group) is assumed to be 0.2381 under the null hypothesis and 0.47619 under the alternative hypothesis. The proportion in group 2 (the control group) is 0.2381. The test statistic used is the two-sided Z-Test with pooled variance. The significance level of the test is 0.05.

Dropout-Inflated Sample Size

	Sample Size			Dropout-Inflated Enrollment Sample Size			Expected Number of Dropouts		
Dropout Rate	N1	N2	N	N1'	N2'	N'	D1	D2	D
20%	63	63	126	79	79	158	16	16	32



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Tests for Two Proportions

Definitions

Dropout Rate (DR) is the percentage of subjects (or items) that are expected to be lost at random during the course of the study and for whom no response data will be collected (i.e., will be treated as "missing").

N1, N2, and N are the evaluable sample sizes at which power is computed. If N1 and N2 subjects are evaluated out of the N1' and N2' subjects that are enrolled in the study, the design will achieve the stated power.

N1', N2', and N' are the number of subjects that should be enrolled in the study in order to end up with N1, N2, and N evaluable subjects, based on the assumed dropout rate. After solving for N1 and N2, N1' and N2' are calculated by inflating N1 and N2 using the formulas N1' = N1 / (1 - DR) and N2' = N2 / (1 - DR), with N1' and N2' always rounded up. (See Julious, S.A. (2010) pages 52-53, or Chow, S.C., Shao, J., Wang, H., and Lokhnygina, Y. (2018) pages 32-33.)

D1, D2, and D are the expected number of dropouts. D1 = N1' - N1, D2 = N2' - N2, and D = D1 + D2.

Procedure Input Settings

Autosave Inactive

Design Tab

Solve For:	Sample Size
Power Calculation Method:	Normal Approximation
Alternative Hypothesis:	Two-Sided
Test Type:	Z-Test (Pooled)
Power:	0.80
Alpha:	0.05
Group Allocation:	Equal (N1 = N2)
Input Type:	Proportions
P1 (Group 1 Proportion|H1):	0.476190476
P2 (Group 2 Proportion):	0.238095238

5. Detailed Study Content

5.1 Overall Study Design:

Project Title: The Effect of Repetitive Transcranial Magnetic Stimulation Combined with Pinaverium Bromide or Bifidobacterium versus Sham Stimulation on Chronic Visceral Pain in Patients with Diarrhea-Predominant Irritable Bowel Syndrome: A Randomized, Controlled Factorial Design Study

Study Type: Prospective 2*2 factorial designed randomized controlled study

This is a multicenter, prospective, 2*2 factorial designed randomized controlled study[19] evaluating the effectiveness of TMS for treating irritable bowel syndrome. This study will recruit and screen subjects according to ethical review standards. Subjects will be randomly divided into an rTMS stimulation + pinaverium bromide treatment group, an rTMS stimulation + bifidobacterium treatment group, a pinaverium bromide + sham rTMS treatment group, and a bifidobacterium + sham rTMS stimulation group for clinical trials. Pain and stool characteristics will be assessed after 2 weeks of treatment, and data will be collected and analyzed finally. This study aims to deeply explore the clinical efficacy of Transcranial Magnetic Stimulation (TMS) on chronic visceral pain in patients with Irritable Bowel Syndrome (IBS), in order to provide more reliable and effective therapeutic targets for clinical application.

5.2 Subject Grouping

Intervention measures (Including whether the investigational drugs are used off-label. If used

off-label, the safety and necessity of the research must be justified, and the off-label use must be detailed in the informed consent form.)

(1) IBS-D patients receiving rTMS stimulation + pinaverium bromide treatment

rTMS stimulation: 1 Hz, 80% MT, 20 min/d, once daily for 2 weeks;

Pinaverium bromide: Oral, 3 times daily, 1 tablet/time, for 2 weeks;

(2) IBS-D patients receiving rTMS stimulation + bifidobacterium treatment

rTMS stimulation: 1 Hz, 80% MT, 20 min/d, once daily for 2 weeks;

Probiotic: Oral, 2 times daily, 4 capsules/time, for 2 weeks;

(3) IBS-D patients receiving Sham rTMS stimulation + pinaverium bromide treatment

Sham rTMS treatment: 0 Hz, 0% MT, 20 min/d, once daily for 2 weeks;

Pinaverium bromide: Oral, 3 times daily, 1 tablet/time, for 2 weeks;

(4) IBS-D patients receiving Sham rTMS stimulation + bifidobacterium

Sham rTMS stimulation: 0 Hz, 0% MT, 20 min/d, once daily for 2 weeks;

Probiotic: Oral, 2 times daily, 4 capsules/time, for 2 weeks;

Dose Selection/Adjustment

rTMS stimulation: 1 Hz, 80% MT, 20 min/d, once daily for 2 weeks;

Pinaverium bromide: Oral, 3 times daily, 1 tablet/time, for 2 weeks;

Probiotic: Oral, 2 times daily, 4 capsules/time, for 2 weeks;

Administration Time

This study adopts a standardized administration time scheme to ensure treatment consistency: Pinaverium bromide (50mg) is taken orally 30 minutes before meals three times daily, Bifidobacterium (500mg) is taken after breakfast and before bedtime, both study drugs are dispensed with electronic medication boxes (MediSafe system) for timed reminders and medication recording.

Blinding/Unblinding

Blinding method: rTMS real/sham stimulation uses identical equipment and operating sounds, administered by an independent technician through an encrypted control system; drugs (pinaverium bromide/bifidobacterium) use matching placebos (identical capsules, boxes, labels),

distributed uniformly by the central pharmacy according to random codes; 2) Statistical unblinding: Unblinding is performed in two stages after database lock -- first, an independent statistician performs inter-group comparisons (Group A vs. B vs. C vs. D), the final reveal of the intervention corresponding to each group occurs after the main conclusions are formed; 3) Quality control: Blinded assessment is conducted monthly, accidental unblinding events must be recorded within 48 hours and the impact on the study assessed.

Rescue Medication and Supportive Therapy (Necessary treatment measures when SAEs related to the study occur)

This study establishes strict norms for rescue medication and supportive therapy: 1) rTMS-related SAE: Seizure - immediately stop stimulation and intravenous push diazepam (5-10mg), transfer persistent convulsions to neurological ICU for monitoring; Severe headache/dizziness - administer paracetamol (≤1g/dose) combined with vestibular inhibitors; 2) Drug-related SAE: Pinaverium bromide allergic reaction - immediately discontinue drug and intramuscular injection of adrenaline (0.3-0.5mg, 1:1000), oral loratadine (10mg/day); Bifidobacterium-induced bacteremia - immediately stop administration and intravenous infusion of vancomycin (15mg/kg q12h) combined with blood culture-guided treatment; 3) Psychological support: Worsening anxiety/depression (HADS score increase ≥8 points) - refer to psychological department for intervention. All SAE treatments are executed by the research center's 24-hour emergency team, using standardized (emergency kits) (containing the above drugs and rescue equipment), the treatment process involves continuous ECG monitoring and recording of vital sign changes. Costs of rescue medication are covered by research insurance, subsequent medical follow-up for subjects continues until symptoms completely resolve + 2 weeks. After SAE resolution, the causal relationship with the intervention measures is assessed by an independent medical committee, major SAEs (e.g., anaphylactic shock) require re-evaluation of the individual's risk-benefit ratio for continuing the study. All rescue measures are recorded in the source documents and synchronized to the eCRF system, serving as key data for safety analysis.

6. Study Implementation Procedures

Subject Management

Subject recruitment methods: Establish open and transparent channels, publish recruitment information approved by the Ethics Committee, post recruitment advertisements, etc., so that patients with potential enrollment opportunities can directly contact the researchers.

Informed consent process: Include privacy protection in the informed consent form, fully inform the subjects, obtain their consent, so that subjects know their personal information and privacy are protected by law and the research team will use it reasonably according to legal provisions and the requirements of documents such as the informed consent form. Once it is found that the subject's personal information or privacy is violated, the subject can raise questions or even resort to legal means, and these actions will not affect normal clinical diagnosis and treatment.

Screening number allocation

Take confidentiality measures to ensure the confidentiality of research project materials, such as using codes to mark subject identification information. The subject's name and other identifying information should be replaced with a "subject identification code" to ensure that identity information, disease information, biological sample information, and other data are provided to other trial researchers after encoding processing; use subject identification codes on case report forms;

Post-treatment visits (Safety follow-up visits, follow-up visits, survival follow-up)

This study designs a comprehensive post-treatment follow-up system to ensure long-term efficacy and safety assessment: a 12-week follow-up period is conducted after the last treatment.

7. Research Data Management and Statistical Analysis.

This study adopts strict data management and statistical analysis methods to ensure the scientificity and reliability of the randomized controlled factorial design study.

8. References

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