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Acupuncture combined with Chinese herbal medicine for discogenic low back pain: protocol for a multicentre, randomised controlled trial

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ABSTRACT

Introduction Discogenic low back pain is a common form of chronic low back pain. In traditional Chinese medicine, combinations of acupuncture and herbal medicine are frequently used to manage this condition. However, evidence for the efficacy of a combined approach remains scarce. To address this gap, we designed a multicentre, randomised controlled trial to compare the effects of the combined use of acupuncture and Chinese herbal medicine, and their separate applications along with non-steroidal anti-inflammatory drugs, in treating discogenic low back pain.

Methods and analysis This is a multicentre, prospective, randomised, four-arm, parallel-controlled trial involving patients with discogenic low back pain. Patients will be randomly divided into four groups (acupuncture combined with herbal medicine, acupuncture, herbal medicine and positive drug control) at a 1:1:1:1 ratio. All patients will undergo a 4-week treatment regimen consisting of acupuncture (active or sham acupuncture) and oral medication (herbal medicine or placebo granules and celecoxib or placebo capsules), as well as a 3-month follow-up assessment. The primary outcome measure will be pain intensity, measured using the Visual Analogue Scale after a 4-week treatment period. Secondary outcome measures will include the lumbar pressure pain threshold, pain-related disability measured using the Oswestry Disability Index, Hospital Anxiety and Depression Scale, Pittsburgh Sleep Quality Index, 36-Item Short-Form Health Survey and incidence of adverse events. Assuming an SD of 1.8, minimal clinically important difference of 1.5 and a 10% dropout rate, at least 97 participants per group are needed, totalling 388 participants.

Ethics and dissemination The study was approved by the Ethics Committee of Dongzhimen Hospital Affiliated with Beijing University of Chinese Medicine (approval number: 2024DZMEC-083-03) and the other seven participating subcentres. All participants will provide written informed consent. This trial will be conducted in accordance with the principles outlined in the Declaration of Helsinki and its amendments. This work will be disseminated through the publication of peer-reviewed manuscripts.

Trial registration number ChiCTR2400082428.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This will be a multicentre, four-arm, randomised controlled trial.
⇒ The study will involve the consistent administration of the three intervention modalities across all groups using a systematically paired placebo.
⇒ Implements a rigorous two-tiered blinding strategy and centralised randomisation.
⇒ The absence of a standalone placebo control group precludes the evaluations of the placebo effect.
⇒ Due to the particularity of acupuncture procedures, it is difficult to blind the acupuncturist of this study.

INTRODUCTION

Discogenic low back pain is a common type of chronic low back pain caused by abnormalities in the internal structure and metabolic function of the intervertebral disc, typically manifested as disc degeneration and annular fibrosis rupture.[1] A prospective clinical study with a 4-year follow-up indicated that the natural course of discogenic low back pain is slow and persistent, with approximately 67.2% of patients experiencing no improvement in pain and functional impairment, significantly impacting their quality of life and work efficiency.[2]

The majority of patients can opt for conservative treatment, involving both non-pharmacological and pharmacological interventions.[1 3] Among pharmacological interventions, non-steroidal anti-inflammatory drugs (NSAIDs) are recommended as the first-line therapy for chronic low back pain,[4] offering effective pain relief and anti-inflammatory effects through oral administration, which allows convenient self-treatment at home. However, their long-term use is limited by adverse reactions and drug tolerance.[5] In China, herbal medicine is also used for managing chronic pain.[6 7] Chinese herbal medicine benefits from minimal side

effects, multiple targets, multiple pathways and no drug tolerance, enabling long-term usage.[8] Herbal formulas are composed of multiple medicinal herbs, exerting a holistic therapeutic effect.[9 10] They could simultaneously improve various symptoms or conditions associated with chronic pain, such as depression, anxiety and sleep disorders[11] and reduce dependence on pharmacological interventions. The American College of Physicians clinical practice guidelines strongly recommend non-pharmacological therapy as the first-line treatment for patients with chronic low back pain, including exercise, multidisciplinary rehabilitation and acupuncture.[4]

Acupuncture, a hallmark therapy in traditional Chinese medicine, can exert analgesic effects, without the adverse effects and dependency associated with medications.[12–15] It has been included in the clinical practice guidelines for low back pain in several countries.[4 16 17] To achieve better and more enduring pain management outcomes, clinicians often combine acupuncture with Chinese herbal medicine, leveraging the strengths of both modalities to reduce the medication dosage and side effects, enhance patient compliance and improve treatment efficacy.[18–21] Our previous study has shown that in patients with chronic pain primarily manifesting as knee joint pain, acupuncture combined with low-dose Chinese herbal medicine treatment provides better pain relief, improves quality of life and alleviates anxiety and depression compared with outcomes using acupuncture or Chinese herbal medicine alone.[22]

However, few clinical studies have evaluated the combined use of acupuncture and Chinese herbal medicine for the treatment of discogenic low back pain. Studies are limited to the Chinese literature, and there is a lack of sufficient evidence to demonstrate the superiority of the combined approach over acupuncture, Chinese herbal medicine or NSAIDs alone in the treatment of discogenic low back pain. Therefore, this prospective, multicentre, randomised, four-arm parallel-controlled trial was designed to evaluate the clinical efficacy and safety of acupuncture combined with Chinese herbal medicine in the treatment of discogenic low back pain from multiple perspectives, including pain, pain-related disability, mood, sleep, health status and the incidence of adverse events. This study aims to provide high-quality evidence for clinical practitioners to choose treatment strategies based on evidence-based medicine.

METHODS AND ANALYSIS

Study design

This study will be a prospective, multicentre, randomised, parallel-controlled trial involving patients with discogenic low back pain. A total of 388 patients will be randomly divided into four groups at a 1:1:1:1 ratio.

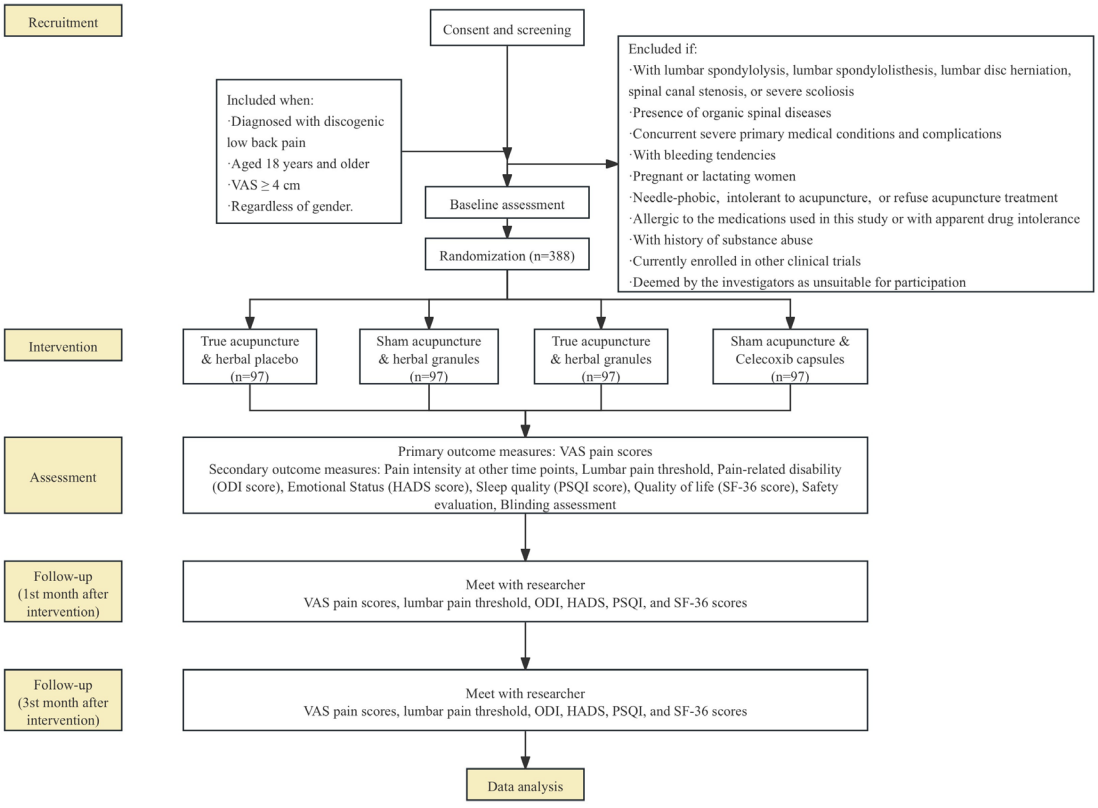

Figure 1 Flow chart followed the checklist of Standard Protocol Items: Recommendations for Interventional Trials showing patient enrolment, allocation, treatment and follow-up of participants. HADS, Hospital Anxiety and Depression Scale; ODI, Oswestry Disability Index; PSQI, Pittsburgh Sleep Quality Index; SF-36, 36-Item Short-Form Health Survey; VAS, Visual Analogue Scale.

Figure 1 shows a flow chart of the study design. Standard Protocol Items: The Recommendations for Interventional Trials checklist is provided in online supplemental file 3.

Study sites and recruitment procedures

This clinical trial will be conducted at eight tertiary hospitals in China. Patients can obtain relevant information about the trial and contact information for researchers through online platforms and recruitment posters posted in hospitals. Doctors will conduct patient examinations to assess whether they meet the inclusion criteria. Additionally, all patients with discogenic low back pain who visit the orthopaedic, acupuncture, massage or pain clinics at the hospital will be asked if they are willing to participate in this trial. Participants who underwent MRI of the lumbar spine within the previous 6 months will be screened, and blood tests for liver and kidney function will be performed before enrolment.

Study population and inclusion/exclusion criteria

This trial will recruit voluntary participants aged 18 years and older, diagnosed with discogenic low back pain, regardless of gender, with a Visual Analogue Scale (VAS) ≥4 cm. The diagnosis of discogenic low back pain should be made by orthopaedists, acupuncture doctors or pain management specialists with at least a bachelor's degree in medicine. According to Kim *et al*[23] and Peng *et al*,[24] the diagnostic criteria for discogenic low back pain are as follows: recurrent low back pain lasting more than 6 months but without signs of nerve root compression; primary manifestation is continuous pain at the midline of the lumbar region, possibly accompanied by buttock or lower limb heaviness but generally not extending beyond the knee; Magnetic Resonance Imaging T2 Weighted Imaging 1 (T2W1) showing reduced intervertebral disc signal ('black disc' signal) with or without small round or oval high-intensity zones adjacent to the posterior midline of the intervertebral disc on T2W1 sagittal images.

Patients meeting one or more of the following criteria will be excluded from the trial: (1) with lumbar spondylolysis, lumbar spondylolisthesis, lumbar disc herniation, spinal canal stenosis or severe scoliosis; (2) presence of organic spinal diseases, such as fractures, tuberculosis, tumours and ankylosing spondylitis; (3) concurrent severe primary medical conditions and complications, such as severe liver or kidney disease, severe heart disease or poorly controlled hypertension, poorly controlled diabetes (Hemoglobin A1c, Hba1c>9%), severe gastrointestinal diseases or severe digestive system problems; (4) with bleeding tendencies; (5) pregnant or lactating women; (6) needle-phobic, intolerant to acupuncture or refuse acupuncture treatment; (7) allergic to the medications used in this study or with apparent drug intolerance; (8) a history of substance abuse (includes alcohol abuse, as defined by the DSM-5 criteria); (9) currently enrolled in other clinical trials and (10) deemed by the investigators as unsuitable for participation in the study.

Randomisation and blinding methods

A central randomisation method will be employed to ensure complete random allocation and concealment. The blinding design will employ a two-tiered approach. The first tier will involve group codes (groups A–D), and the second tier will entail treatment modalities corresponding to each group code. We will use the numbers 1 and 2 to denote the herbal and placebo granules and letters A and B to denote celecoxib and placebo capsules, respectively. Only the project manager will know the actual correspondence between the codes.

We will use ResMan Research Manager (www.medresman.org.cn) to implement central randomisation and allocation concealment. ResMan is an internet-based public clinical trial data collection and management system (Electronic Data Capture System, EDC System) established by the Chinese Clinical Trial Registry. The project manager creates the project in this system, sets up subcentres, sample sizes and group codes, selects the option to automatically generate random numbers and uses random numbers to publicly disclose grouping information. A password known only to the project manager will be set to request the group codes. The project manager will issue a unique data entry account to each centre. Researchers can log in to these accounts to enter participant information and perform randomisation. Data entry accounts can only view the participants entered by the particular centre and their corresponding random numbers; group codes are concealed and visible only to the project manager. The project manager will allocate interventions to patients based on group codes and will send acupuncture and medication plans to the respective acupuncturists and pharmacists via SMS.

Before unblinding, only the project manager will know the group codes and the corresponding treatment methods. The case report form (CRF) will only include data for a random number of the participants. Patients, outcome assessors and statisticians will be blinded to treatment allocation. Acupuncturists will only know the acupuncture intervention plan (active or sham acupuncture) and pharmacists will only know the medication plan (herbal granule 1 or 2 and capsule A or B).

First-tier unblinding will be conducted during data analyses, whereas second-tier unblinding will be performed during the efficacy comparison. For safety reasons, unblinding may be necessary in cases of severe adverse events or side effects that require immediate management, enabling appropriate measures to be taken.

Grouping and intervention

Patients will be allocated to four groups (acupuncture combined with Chinese herbal medicine, acupuncture, Chinese herbal medicine and positive drug control groups). All participants in the four groups will undergo a 4-week treatment regimen consisting of acupuncture and oral medication as well as a 3-month follow-up. Specifically, the acupuncture combined with Chinese herbal medicine group will receive electroacupuncture and

Table 1 Differences among three acupuncture groups

	Acupuncture combined with herbal medicine group	Acupuncture group	Herbal medicine group	Positive drug control group
Acupuncture	Active acupuncture	Active acupuncture	Sham acupuncture	Sham acupuncture
Points stimulated	Acupoints	Acupoints	Non-acupoints	Non-acupoints
Puncturing the skin	Yes	Yes	No	No
De qi	Yes	Yes	No	No
Electrical apparatus	Attached	Attached	Attached	Attached
Electric current	Yes	Yes	No	No
Granules	Herbal granules	Placebo granules	Herbal granules	Placebo granules
Capsules	Placebo capsules	Placebo capsules	Placebo capsules	Celecoxib capsules

Chinese herbal medicine granules along with placebo capsules; the acupuncture group will receive electroacupuncture along with granule and capsule placebos; the herbal medicine group will receive Chinese herbal medicine granules along with sham acupuncture and capsule placebo and the positive drug control group will receive celecoxib capsules along with sham acupuncture and granule placebo (table 1).

Acupuncture protocol

Active Acupuncture

- The selected acupoints are as follows: the bilateral Shenshu (BL23), bilateral Dachangshu (BL25), bilateral Weizhong (BL40) and Ashi points (the most tender point in the lumbar region). All acupoints will be located according to the WHO standard acupuncture point locations, as shown in table 2.
- Acupuncturists will first apply circular foam pads with a diameter of 1 cm on the corresponding acupoints and then insert a disposable sterile acupuncture needle (0.30×40 mm) vertically through the foam pads into the subcutaneous tissue, penetrating approximately 26–32 mm.
- The acupuncturist will twist the needle handle to achieve de qi (feeling of heaviness and tightness around the needle site) and then connect the paired electrodes of the electroacupuncture device to the handles of the Shenshu (BL23) and Dachangshu (BL25) points on the same side. The waveform will be set to sparse-dense waves, frequency to 2/100 Hz and duration to 30 min, and the current intensity will be increased gradually until the needle trembles slightly.

Sham acupuncture

- The stimulation sites are non-acupoints in the lumbar region located 5 cun lateral to the lower border of the second lumbar vertebra (L2), 5 cun lateral to the lower border of the fourth lumbar vertebra (L4), 3 cun above the midpoint of the popliteal crease and 3 cun above the Ashi point.
- The acupuncturist will apply circular foam pads with a diameter of 1 cm to the stimulation sites and then vertically insert a custom-made blunt needle (0.4×25 mm) through the foam pad without puncturing the skin.
- The acupuncturist will twist the needle handle by 10 rotations for each stimulation site and then connect the paired electrodes of the electroacupuncture device without current output to the handles of the non-acupoint points corresponding to the same-side Shenshu (BL23) and Dachangshu (BL25). The parameters are identical to those used for active acupuncture.

Both active and sham acupuncture treatments will be administered three times per week, with at least a 1-day interval and a maximum 2-day interval between each treatment session, for a total of 4 weeks.

Table 2 Locations of acupoints for active acupuncture

Acupoint	Location
Shenshu (BL23)	In the lumbar region, at the same level as the inferior border of the spinous process of the second lumbar vertebra (L2), 1.5 B-cun lateral to the posterior median line.
Dachangshu (BL25)	In the lumbar region, at the same level as the inferior border of the spinous process of the fourth lumbar vertebra (L4), 1.5 B-cun lateral to the posterior median line
Weizhong (BL40)	On the posterior aspect of the knee, at the midpoint of the popliteal crease.
Ashi point	The point where the patient feels most pain

B-cun: proportional bone (skeletal) cun. Using joints on the surface of the body as the primary landmarks, the length and width of every body part is measured by such proportions. In the back and lumbar region, the 1.5 B-cun of the back point is 1/2 width of the median spine from the medial edge of the scapula.

Table 3 Herbal name and part(s) used

Chinese name	English name	Latin name	Part(s) used	Proportion (%)
Xixiancao	Siegesbeckia herb	Siegesbeckia orientalis L.	Rhizomes	18.75
Baishao	white peony root; peony	Paeonia lactiflora Pall.	Roots	37.5
Yanhusuo	Corydalis Yanhusuo	Corydalis Rhizoma	Rhizomes	18.75
Weilingxian	Clematis chinensis	Clematidis Radix et Rhizoma	Rhizomes and roots	18.75
Gancao	liquorice root	Glycyrrhiza uralensis Fisch.	Rhizomes and roots	6.25

Chinese herbal medicine granules and placebo granules

The Chinese herbal formula used in this study will be a clinical analgesic formula consisting of the following five herbs in a 3:6:3:3:1 ratio: Xixiancao (Siegesbeckia orientalis L.), Baishao (Paeonia lactiflora Pall), Yanhusuo (Corydalis Rhizoma), Weilingxian (Clematidis Radix et Rhizoma) and Gancao (Glycyrrhiza uralensis Fisch.). The herbal medicine components are listed in table 3. Beijing Kangrentang Pharmaceutical will be commissioned to prepare the Chinese herbal medicine granules and corresponding placebos with a similar appearance and odour. Granules will be administered at a dosage of 10.68 g per day.

Chinese herbal granules and placebo granules will be taken orally after breakfast and dinner, twice daily, with one sachet each time and intake will continue for 4 weeks.

Positive drug and placebo capsules

The positive control drug will be capsules containing celecoxib as the main active ingredient. Celecoxib capsules are selective NSAIDs that exert analgesic and anti-inflammatory effects by inhibiting prostaglandin synthesis. A pharmaceutical company will be commissioned to prepare placebo capsules with an appearance identical to that of celecoxib capsules.

Celecoxib and placebo capsules will be taken orally once daily (0.2 g/capsule, 1 capsule per time) after breakfast for 4 weeks.

The intervention will be terminated for participants in the treatment process under the following circumstances: (1) occurrence of severe adverse events and (2) complete disappearance of symptoms during treatment.

The researchers will provide clear guidance to the participants, including instructions on experimental procedures, compliance and methods for recording data. Ensuring that the participants understand what they need to do and why they need to do it will enhance compliance with the intervention protocol.

During the 4-week treatment period, the use of medications other than those provided by this study for treating discogenic low back pain will not generally be permitted, but medications for other disorders will be permitted. If a participant experiences intolerable low back pain, they may use the emergency medications (such as ibuprofen, paracetamol, tramadol extended-release tablets, compound paracetamol and dihydrocodeine tablets) and should inform the researcher about their usage. The researcher will accurately record this information on a CRF. Other therapies for discogenic low back pain, such as physical therapy, massage, cupping, or moxibustion, will also be prohibited.

During the 3-month follow-up period following the end of the treatment phase, participants may use medication or undergo treatment for discogenic low back as needed. However, they must report to researchers and accurately record their medication and treatment details.

Outcome measurement

Primary outcome

The primary outcome measure is improvement in low back pain intensity from baseline to week 4, measured using the VAS on the 28th day (±1 day).

The VAS is the most widely used unidimensional tool for assessing pain intensity. The scale primarily consists of a 100 mm line, with one end indicating 'no pain at all' and the other end indicating 'worst imaginable pain' or 'pain to the extreme' among other descriptors. Patients will be asked to mark the point on the line that corresponds to the average intensity of pain they experienced in the previous week, typically using a ' | ' or an 'X.'. According to international expert consensus, the minimal clinically important difference (MCID) in low back pain intensity, as measured by the VAS, is 15 mm.[25]

Secondary outcomes

Pain intensity at other time points: Low back pain intensity will be measured at baseline and at weeks 1, 2, 3, 8 and 16.

Lumbar pressure pain threshold: Pressure algometry is a reliable measure of pain in muscles, joints, tendons and ligaments. The Pain Test FPX Algometer (Wagner) will be used to measure the lumbar pressure pain threshold at baseline and at weeks 1, 2, 3, 4, 8 and 16.

Pain-related disability: Pain-related disability will be assessed using the Oswestry Disability Index (ODI) at baseline and at weeks 1, 2, 3, 4, 8 and 16. The ODI is commonly used to assess functional disability due to low back pain. It consists of 10 questions, each with 6 response options. The total score ranges from 0 to 100 points, with higher scores indicating a greater impact of low back pain on daily life function.

Emotional status: The emotional status of the participants will be assessed at baseline and at weeks 4, 8 and 16 using the Hospital Anxiety and Depression Scale, which

can simultaneously assess anxiety and depression statuses. Higher scores indicated more significant symptoms of anxiety or depression.

Sleep quality: Sleep quality will be evaluated at baseline and at weeks 4, 8 and 16 using the Pittsburgh Sleep Quality Index. The total score ranges from 0 to 21 points. Higher scores indicate poorer sleep quality.

Quality of life: Quality of life will be assessed at baseline and at weeks 4, 8 and 16 using the MOS 36-item Short Form Health Survey (SF-36). The total SF-36 score ranges from 0 to 100 points. A higher score indicates better physical and mental health and quality of life.

Safety evaluation: Patients, assessors and acupuncturists will use specific questionnaires to record all adverse events throughout the trial. Adverse events will be categorised as treatment related or unrelated by acupuncturists and relevant experts within 24 hours of their occurrence. The rates of adverse events, rates of adverse events of different severity and treatment-related adverse events will be calculated for each group. Liver and kidney function tests were performed using serum samples at baseline and after 4 weeks of treatment.

Blinding assessment: To establish successful blinding, participants will be asked to guess the type of intervention they received at weeks 2 and 4.

Study assessment

Screening and baseline assessment will include inclusion and exclusion criteria, study recruitment and informed consent procedures, and assessment of primary and secondary outcome measures. All patients will undergo baseline assessment within one week of treatment initiation. The treatment phase of the study will span 2 weeks, followed by a 3-month follow-up period. The assessment contents and time points during both the treatment and follow-up phases are shown in figure 2.

Patient and public involvement

The patients and the public were not involved in the formulation and design of the research protocol. The

	Study period						
	Baseline	Treatment				Follow-up	
Activities	-7~0 day	week 1	week 2	week 3	week 4	week 8	week 16
Enrolment							
Informed consent	•						
Eligibility screen	•						
Allocation	•						
Socio-demographic characteristics	•						
Medical history	•						
VAS pain score	•	•	•	•	•	•	•
Lumbar pressure pain threshold	•	•	•	•	•	•	•
ODI score	•	•	•	•	•	•	•
HADS score	•			•		•	•
PSQI score	•			•		•	•
SF-36 score	•			•		•	•
Adverse events		•	•	•	•		
Serum liver and kidney function tests	•				•		
Blinding assessment			•		•		

Figure 2 Schedule of enrolment, interventions and assessments. HADS, Hospital Anxiety and Depression Scale; ODI, Oswestry Disability Index; PSQI, Pittsburgh Sleep Quality Index; SF-36, 36-Item Short-Form Health Survey; VAS, Visual Analogue Scale.

research findings will not be disseminated to participants. If the participants expressed interest in the research results, relevant information will be provided after the study is concluded.

Sample size calculation

This study is a parallel-designed randomised controlled trial. Improvement in low back pain intensity measured using the VAS from baseline to 4 weeks post-treatment is the primary outcome measure.

Sample size calculations were performed by using PASS 2021 (V.21.0.3) with multiple comparisons selected. A two-sided α of 0.05 and a power of 90% were set. Based on international expert consensus,[25] the MCID in VAS pain intensity in low back pain was 1.5. Assuming an intragroup SD of 1.8, the average sample size was 87. Considering a dropout rate of 10%, each group must include at least 97 participants, and a total of 388 participants are required for the study.

Data collection and management

To ensure the integrity of data collection, we devised a paper-based CRF for individual patients including all pertinent patient-reported information, assessment scales, and clinician-inspected and recorded details. Each patient will be assigned a unique identifier to preserve the blinding integrity of evaluators and data analysts.

Data will be managed by the principal investigator using the ResMan Clinical Trial Public Management Platform. Following the assessments, the CRF will be meticulously completed by the assessor. After a thorough examination by monitors, they will be independently entered into the clinical trial management platform by two designated data entry personnel; each entry will be conducted twice to ensure accuracy. A data manager will then conduct comprehensive verification. Researchers will continue to scrutinise the data collection progress and study outcomes to promptly address emerging issues.

On the completion of data entry and verification, as stipulated, the original CRF will be systematically archived in a numerical sequence with accompanying retrieval indices for reference purposes. Electronic data files, including databases, examination and analysis protocols, coding manuals, and explanatory documents will be organised meticulously and stored with redundant backups across diverse storage media to safeguard against loss or damage and ensure data integrity and security.

Monitoring and quality control

A third-party contract research institution (Beijing Shi Yuan Medical Technology) will be responsible for monitoring and quality control. Clinical monitors conduct on-site visits to each research centre every 3 months, sample and verify raw data, and regularly convene meetings to address specific issues arising from their work. They provide timely feedback to the principal investigators and methodological experts through monitoring reports and study briefs.

The principal investigators will conduct an interim analysis when half of the recruitment is completed and decide whether to terminate the trial based on the results of the interim analysis.

Adverse events will be recorded after patient enrolment. If serious adverse events potentially related to the intervention measures in this study are suspected, the principal investigator will promptly suspend the study for individual participants and report the findings to the ethics committee.

Data analysis plan

1. Statistical Analysis Software: SPSS V.26.0
2. Level of significance: Two-tailed test, α=0.05, with p<0.05 indicating statistical significance.
3. Statistical analysis populations.

Intention-to-treat (ITT) analysis: All patients were randomised into treatment groups and received at least one treatment session according to the study protocol. An ITT analysis will be conducted to assess both efficacy and adverse events. In cases with incomplete treatment observations, the last observation data will be used as the final study outcome.

Full analysis set (FAS): This represents the ideal population of subjects that is as closely aligned with the ITT principle as possible. This dataset will be derived by excluding participants from a randomised population using minimal and rational methods.

Per-protocol set (PPS): The PPS is also known as the efficacy set, effective sample or valuable case sample. It comprises data derived from a subset of cases that fully comply with the study protocol and represents a subset of the FAS. Compliance includes considerations such as the treatment received, feasibility of primary endpoint measurement and lack of major protocol violations.

Safety analysis set (SS): For safety evaluation purposes, the subject set used for summarisation is called the SS. This set will include all participants who underwent at least one treatment session after randomisation.

4. Inclusion and completion status.

In the ITT analysis, we will consider the frequency of cases for enrolment, protocol deviations, dropout cases and completion of the entire trial.

5. Baseline equivalence analysis.

A PPS analysis will be conducted to compare demographic data. Descriptive statistics for continuous data will be presented as the mean±SD, while categorical data will be presented as frequencies (percentages). Other baseline indicators will be expressed as the mean±SD and analysed using analysis of variance. Categorical variables (including ordinal categorical variables) will be analysed using the χ^2 test or rank-sum test based on the research hypothesis.

6. Treatment compliance analysis.

An ITT analysis will be used to calculate compliance based on the actual number of treatments received. Patients who received treatment sessions equal to or greater than 80% (including 80%) were considered to

have good compliance. The formulas for compliance calculation were as follows: acupuncture treatment compliance (%)=(actual number of treatment sessions received by subjects/12 treatment sessions)×100; Chinese herbal medicine treatment compliance (%)=(actual number of doses taken by subjects/28 doses)×100; Western medicine treatment compliance (%)=(actual number of doses taken by subjects/28 doses)×100.

7. Efficacy analysis.

PPS and FAS analyses will be performed simultaneously for the primary and secondary efficacy endpoints. Owing to the multicentre nature of this clinical trial, the influence of centre effects on efficacy endpoints will be considered during the analysis. For quantitative endpoints approximating a normal distribution, paired t-tests will be used for comparisons of parameters before and after treatment within each group, while ANOVA will be employed to evaluate among-group differences. In cases where the assumption of homogeneity of variance is met, multiple comparisons will be conducted using the least significant difference method.

8. Safety analysis.

An SS analysis will be conducted using χ^2 tests or Fisher's exact tests to compare the incidence rates of adverse events among groups and provide a tabulated description of the adverse events.

9. Blinding analysis.

An IIT analysis will be conducted using both the Bang's Blinding Index and the James Blinding Index to evaluate the effectiveness of blinding.

Data statement

After the end of the trial and publication of the research results, the technical appendix, statistical code and dataset will be made available from the ResMan (www.medrescman.org) clinical trial public management platform.

Ethics and dissemination

Ethics approval

This study adhered to national laws and the Declaration of Helsinki. Ethics approval for this study was obtained from the Ethics Committee of Dongzhimen Hospital Affiliated with Beijing University of Chinese Medicine and the other seven participating subcentres. If significant modifications to the trial protocol are required, the principal investigator will resubmit the protocol for review and approval by the ethics committee.

Consent or assent

Before inclusion in the study, the researchers will orally and comprehensibly explain the study to the patients and voluntary written informed consent will be obtained. Patients had the right to withdraw from the study at any time if they did not wish to continue participating (online supplemental file 1

Confidentiality

Only the research personnel and monitors involved in this trial will have access to the participants' clinical research records. The ethics committee has the authority to access the relevant records of clinical research projects. Data processing will be anonymised, omitting information that can identify individual subjects.

Trial status

The protocol version number and date: V3.0, 18 March 2024. Enrolment plan is to begin in June 2024 and is expected to end in December 2025. At the time of manuscript preparation, enrolment of participants has not yet begun (online supplemental file 2).

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Contributors GT conceived the study and sought funding. YL, XL and LH initiated the study design. XX and TL sought ethical approval. YL prepared the first draft of the manuscript. XL and LH were involved in critical revision of the manuscript. YL and XL revised the manuscript based on comments from editors and reviewers. GT replied to comments on the manuscript. YL, XL, LH, GT, XX and TL contributed to the refinement of the study protocol and approved the final manuscript. YL, XL and LH contributed equally. GT acted as guarantor.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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