Efficacy of acupuncture for treatment of intermittent claudication in patients with degenerative lumbar spinal stenosis

Study Protocol with Statistical Analysis Plan (SAP) and

Informed Consent Form (ICF)

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3. Guangdong Provincial Hospital of Traditional Chinese Medicine
4. The First Hospital of Hunan University of Chinese Medicine
5. The Third Affiliated People's Hospital of Fujian University of Traditional Chinese Medical

Date:

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Confidentiality Statement:

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2.Introduction

Degenerative lumbar spinal stenosis (DLSS) is a condition involving narrowing of the space for the sagittal diameter of the spinal canal or nerve root canal for the spinal nerve or cauda equina secondary to degenerative changes [1-3]. DLSS is a common cause of gluteal and lower extremity pain and more likely to affect women and elderly people aged 60–70 years [4]. Because imaging evidence is not necessarily related to clinical symptoms, there are no specific epidemiological data for DLSS [5, 6]. According to the results of magnetic resonance imaging (MRI), 30–90% of asymptomatic adults may have spinal abnormalities including disc herniation, disc degeneration, or spinal stenosis [7]. DLSS is the most common type of spinal stenosis [1, 8]. The early symptoms of DLSS are soreness and pain in the low back, gluteal region, and posterior region of the thighs, which can be relieved after resting or changing posture. As patients with DLSS experience gradually aggravated symptoms, they may have neurogenic claudication with hypoesthesia and numbness in the lateral lower legs and feet; additionally, some patients may have bowel and bladder disturbances [9, 10]. DLSS patients have a poor quality of life, especially elderly patients [11]. In accordance with the guidelines of the North American Spine Society, treatment options comprise surgical therapy, epidural steroid injections and physical therapy, and transcutaneous electrical stimulation. According to some studies, the long-term efficacy of surgery is not superior to that of non-surgical therapy [12-15]. More studies are required to explore the efficacy of non-surgical therapy [16]. According to a systematic review [17] and recent studies [18, 19], acupuncture may improve the symptoms of patients and thus their quality of life; however, there is a lack of placebo-controlled and large-sample sized studies. More studies with a sufficient sample size are needed to provide evidence of the efficacy of acupuncture for treating DLSS.

3. Study Design and Objective

3.1 Objective

The aim of this study is to assess the effects and safety of acupuncture for relieving predominantly neurogenic claudication pain symptoms in patients with central DLSS.

3.2 Primary Hypothesis

We hypothesize the existence of difference between acupuncture and sham acupuncture (SA) in relieving neurogenic claudication pain symptoms among patients with central DLSS at week 6.

3.3 Study Design and Organizations

This is a multicenter, participants-blinded, parallel-group, randomized controlled study conducted in China.

The participants will be recruited in 5 clinical sites, which are Guang'anmen Hospital, China Academy of Chinese Medical Sciences; Shaanxi Provincial Hospital of Traditional Chinese Medicine; Guangdong Provincial Hospital of Traditional Chinese Medicine; The First Hospital of Hunan University of Chinese Medicine; and The Third Affiliated People's Hospital of Fujian University of Traditional Chinese Medicine. The study design and organization will be responsible by Guang'anmen Hospital, China Academy of Chinese Medical Sciences. A data coordination center will be established at Linkermed Pharm Technology Co., Ltd (Beijing, China) to monitor data management.

3.4 Study Time Frame

The duration of the study for each participant will be 31 weeks: 1 week before randomization as eligibility screening and baseline assessment, 6 weeks of treatment period, and 24 weeks of follow up period after the cessation of treatment (Figure 1. Study Design).

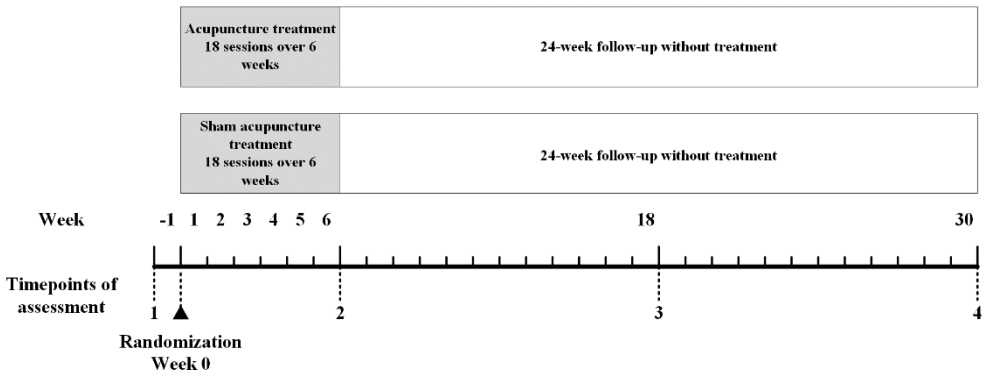

Figure 1. Study Design

There will be four timepoints of assessment:

Timepoint 1 will be scheduled during weeks -1 as eligibility screening and baseline assessment;

Timepoint 2 will be scheduled at week 6 at the end of treatment period;

Timepoints 3 and 4 will be scheduled at weeks 18 and 30, respectively, during 24-week follow-up period.

3.5 Trial Flow Chart

The trial flow chart is shown in Figure 2.

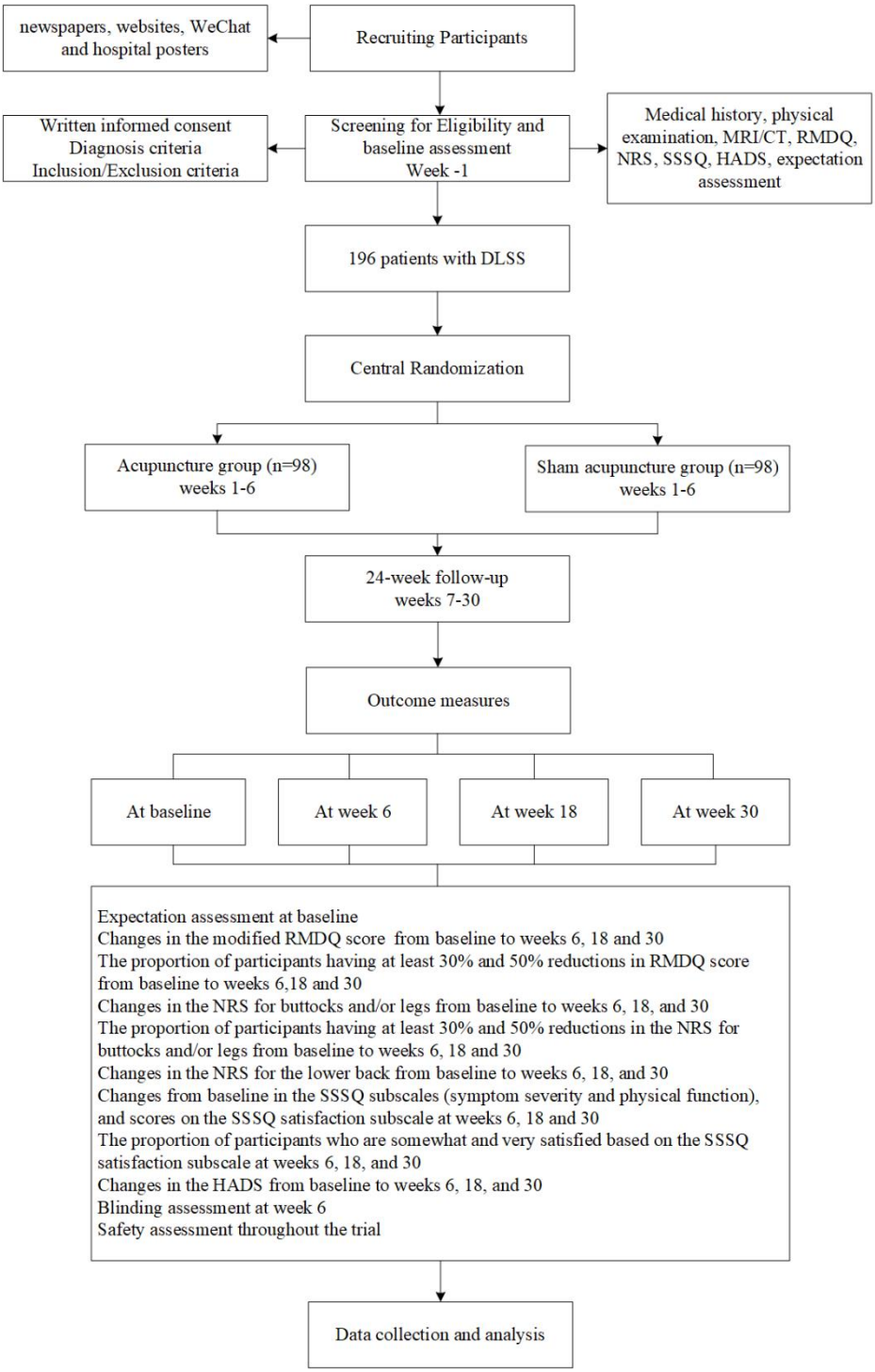

Figure 2. Trial Flow Chart

Abbreviations: DLSS, Degenerative lumbar spinal stenosis; RMDQ, Roland-Morris Disability Questionnaire; NRS, Numerical Rating Scale; SSSQ, Swiss Spinal Stenosis Questionnaire; HADS, Hospital Anxiety and Depression Scale.

4. Study Population

4.1 Diagnosis criteria

The diagnosis of central DLSS is made according to the North American Spine Society (NASS) [3], based on medical history, physical examination and related neuroimaging examination. An orthopedist from each center will be in charge of the diagnosis.

The detailed diagnostic evaluations are listed as following:

(1) Participants should have a medical history of recurrent pain in buttock or lower extremity, with or without back pain.

(2) Neurogenic intermittent claudication is a hallmark of DLSS. This is the tendency for symptoms, usually pain, to be exacerbated with walking, standing, and/or maintaining certain postures, and relieved with sitting or lying. The participants usually walk in a flexed or stooped position to relieve or reduce symptoms.

(3) Neuroimaging examination like MRI or computed tomography (CT) shows structural narrowing of the intraspinal canal.

4.2 Inclusion criteria

Participants will be eligible if they:

(1) Meet the requirements for a clinical diagnosis of DLSS combined with an MRI- or CT-based radiological diagnosis of central sagittal diameter stenosis of the lumbar spinal canal;

(2) Have neurogenic intermittent claudication characterized by progressive pain of the buttocks and/or legs when standing or walking or with extension of the back, which are relieved upon sitting, lying down, or bending forward [20]; they always walk in flexion or hunchback posture;

(3) Have pain of an intensity ≥4 in the buttocks and/or legs when walking, standing, or extending the back, as measured using the Numerical Rating Scale (NRS);

(4) Have pain in the buttock and/or leg that is more severe than their pain in the lower back;

(5) Have a Roland-Morris Disability Questionnaire (RMDQ) score of at least 7;

(6) MRI (mainly) or CT scan showed the anterior posterior diameter of the canal was ≤ 12 mm;

(7) Are aged 50-80 years;

(8) Have provided signed consent and exhibit willingness to participate in the trial.

4.3 Exclusion criteria

Patients will be excluded if they have:

(1) Congenital stenosis of the vertebral canal, indications of surgery for DLSS (e.g., segmental muscular atrophy, bowel and bladder disturbances), spinal instability requiring surgery, lumbar tuberculosis, lumbar metastatic carcinoma, vascular claudication, or vertebral body/vertebral stenosis segment compression fracture;

(2) Severe vascular, pulmonary, or coronary artery disease with limited lower extremities motility;

(3) Clinical comorbidities that could interfere with the collection of data related to pain and walking function such as fibromyalgia, chronic widespread pain, amputation, stroke, Parkinson's disease, spinal cord injury, and dementia;

(4) Cognitive impairment, such that they are unable to understand the content of the assessment

scales or provide accurate data;

(5) A history of lumbar surgery;

(6) Plans to become pregnant within 12 months or are already pregnant;

(7) Received acupuncture treatments for DLSS within the previous 30days;

(8) Neurogenic intermittent claudication mainly manifesting as numbness, weakness, or paresthesia of the lower extremities instead of pain.

5. Subject Recruitment, Screening, Enrolment, and Group Assignment

5.1 Recruitment and Informed Consent

From March 2019 to June 2020, patients with DLSS will be recruited via newspapers, websites, WeChat and hospital posters in 5 centers over China. Patients who show interest in the study and meet the basic criteria of the study will sign the written informed consent form (see Appendix 1 Patient Inform Consent) before the formal screening process. The informed consent form will be reviewed and approved by institutional review boards at Guang'anmen Hospital, China Academy of Chinese Medical Sciences, and individual clinical site.

5.2 Screening and Baseline Assessment

On patients' official screening visit to hospital, they will sign the written informed consent form. Research assistants of each site will record their demographic information, course of disease and previous treatments. Orthopedists are responsible for the diagnosis and the differential diagnosis of DLSS.

Patients will receive a series of procedures to screen for eligibility, which will take approximately one week (week -1). To use the funds rationally and for consideration of the convenience of participants, the procedures will be scheduled step by step (Figure 3. Subject Flow Chart), and the eligibility criteria will be verified timely during the process. Those who fail in one step will not receive further screening.

To ensure the accuracy of eligibility screening and outcome assessment, it is imperative that patients avoid any therapy for DLSS throughout the trial. However, rescue medication can be used for emergency, except 48 hours before the assessment of pain and physical function.

The screening procedures include (in sequence):

(1) The medical history, demographic information, and previous treatments;

(2) Physical examinations;

(3) RMDQ score and NRS score for the buttocks and/or legs, back;

(4) MRI (mainly) or CT.

Participants who are still eligible after the examinations will complete the baseline outcome assessment questionnaires, which include the Swiss Spinal Stenosis Questionnaire (SSSQ), the Hospital Anxiety and Depression Scale (HADS), and participants' expectation assessment. The RMDQ and NRS will be completed again.

Note: Although the eligibility screening and baseline assessment are interpreted as Timepoint of assessment 1, participants might need to visit the hospital more than once during the process. The clinical site can arrange the procedures of examinations in accordance with the rapidity of each examination in their own hospital to save participants' time and visits to hospital.

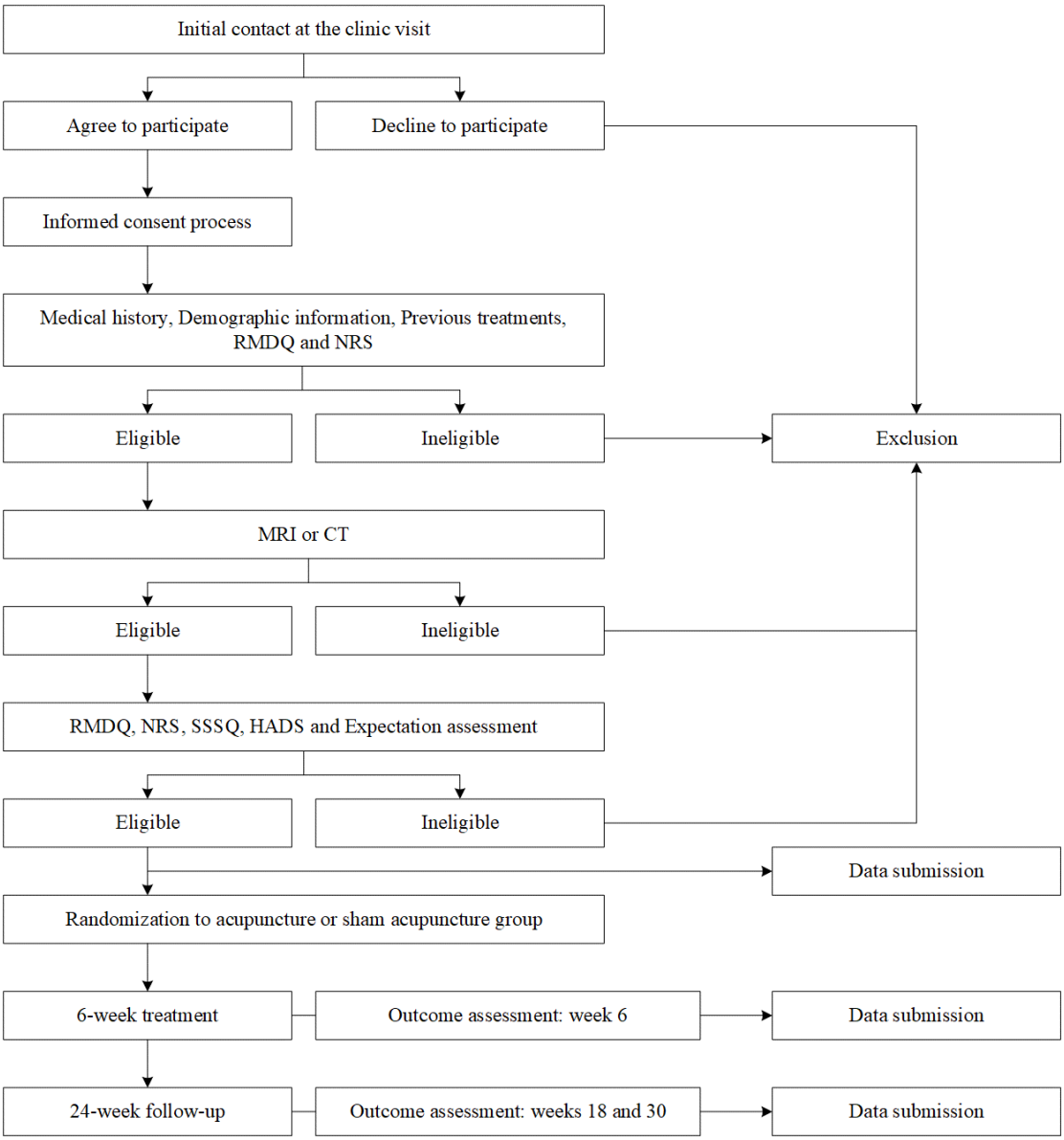

Figure 3. Subject Flow Chart

Abbreviations: RMDQ, Roland-Morris Disability Questionnaire; NRS, Numerical Rating Scale; SSSQ, Swiss Spinal Stenosis Questionnaire; HADS, Hospital Anxiety and Depression Scale.

5.3 Group Assignment

Eligible participants will be randomly assigned either to the acupuncture group or the sham acupuncture (SA) group at week 0. The randomization will be completed by acupuncturists. The details of the central randomization will be described in 6.1 Randomization.

6. Randomization and Blinding

6.1 Randomization

Patients who provide informed consent and are eligible will be randomly assigned at a ratio of 1:1 to either the acupuncture group or the SA group using a central randomization system. The randomization scheme will be generated by Linkermed Pharm Technology Co., Ltd (Beijing, China) using statistical analysis software SAS 9.4 with "proc plan" program. The randomization sequence will be generated in varying block sizes and stratified by center. A comprehensive document describing the randomization scheme will be sealed in opaque envelopes by the staff who produce it and kept by another staff who takes no part in the clinical trial. The randomization scheme will not be checked by anyone except the senior system administrator. In each clinical center, a research assistant who takes no part in the treatment and outcome assessment will log in the web-based central randomization system to assess the random number and group allocation. All randomization will be masked until all data analyses have been conducted.

6.2 Blinding

The patients, outcome assessors, and statisticians will be blinded to the treatment allocation. Only acupuncturists are aware of the group allocation to administrate treatments.

Participants in the SA group will receive minimally invasive, superficial needle insertion of 2-3mm at the same acupoints used as the acupuncture group. Treatment protocol will be similar to that of the acupuncture group, and the acupuncturists will be trained to perform the same needling rituals in both groups. To test the success of blinding, within 5 minutes after treatment (Session 17 or 18) at week 6, participants will be told that there are two kinds of acupuncture methods, which are the traditional acupuncture where the insertion is relatively deep, and the minimal acupuncture where the insertion is relatively shallow; and participants will be randomly assigned to receive traditional acupuncture or minimal acupuncture at 50% chance respectively. Participants will then be asked to answer the question that "Do you think you have received traditional acupuncture in the past weeks?" The participants will be able to choose one of the following options as the answer: "Yes" or "No".

7. Interventions

Sterile disposable steel needles (Hwato, Suzhou, China) will be used, and acupuncturists with at least 2 years of clinical experience will supply the treatment.

7.1 Acupuncture

The acupoints of bilateral Shenshu (BL23), "Dachangshu (BL25)", Weizhong (BL40), Chengshan (BL57), and Taixi (KI3) will be acupunctured. The locations of all acupoints except "BL25" will be based on the World Health Organization (WHO) Standard Acupuncture Locations [21], as displayed in Table 1. "BL25" is located at 1.5 Bone-cun horizontally outward to the spinous process of the fourth lumbar vertebra.

Participants will lie in the prone position and relax. A pillow will be placed under the lower abdomen of the participants, and their hands will be raised above their heads in order to maximize the enlargement of the intervertebral foramen. Prior to acupuncture, 75% alcohol pads will be used to sterilize the skin around the acupuncture points. For "BL25," sterile disposable steel needles (0.3 mm × 75 mm) will be inserted directly to a depth of 50-70 mm until participants feel a sensation similar to electric shock radiating downward to the knees and the posterior lower legs. Then, the needle will be lifted upward for 1-2 mm without manipulation during the treatment. For the other four acupoints (BL23, BL40, BL57, and KI3), the needles (0.3 mm × 40 mm) will be inserted to a depth of 15-30 mm depending on participants' somatotype, gently rotated and lifted three times to achieve the sense of sourness, distention, and heaviness (*deqi*) [22]. It should be noted that the needle at KI3 will be inserted at an angle of 45° obliquely downward. The needles at all points will be retained for 30 minutes with light lifting, thrusting, and twirling every 10 min during each session. Participants will receive 18 treatment sessions given 3 times per week (ideally every other day) for 6 continuous weeks.

Table 1. Summary of the Acupoints' Location

Acupoints	Location	Depth of insertion
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 Bone-cun* lateral to the posterior median line.	15-30 mm
"Dachangshu (BL25)"	In the lumbar region, at the same level as the spinous process of the fourth lumbar vertebra (L4), 1.5 Bone-cun lateral to the posterior median line.	50-70 mm
Weizhong (BL40)	On the posterior aspect of the knee, at the midpoint of the popliteal crease.	15-30 mm
Chengshan (BL57)	On the posterior aspect of the leg, at the connecting point of the calcaneal tendon with the two muscle bellies of the gastrocnemius muscle.	15-30 mm
Taixi (KI3)	On the posteromedial aspect of the ankle, in the depression between the prominence of the medial malleolus and the calcaneal tendon.	15-30 mm

1 Bone-cun ≈ 20 mm

7.2 Sham Acupuncture (SA)

For the SA group, needles of the same size (0.3 mm ×40 mm) will be inserted at the same acupoints used in treatment of the acupuncture group to a depth of 2-3 mm. No manipulation of needles will be conducted. The treatment duration and frequency of sessions for participants in the SA group will be the same as in the acupuncture group.

7.3 Standardization of Treatment

Guang'anmen Hospital will supply single-use, sterile, and disposable acupuncture needles for each participating site.

Two certified acupuncturists will be needed in each site to perform all the treatments, while the 18 sessions of treatment for each participant should be completed by one specific acupuncturist. All acupuncturists in this trial are required to have completed their professional training in acupuncture in universities of Chinese medicine with at least 2 years of clinical experience.

To improve the consistency of treatments, acupuncturists at each site will receive trial-specific (standardized operation procedure) training at the project launching session. The training will include detailed acupuncture points locations and manipulation methods in both the acupuncture and SA groups. A video showing detailed information on how to perform the acupuncture and SA will also be provided.

To avoid the inadvertent unblinding, acupuncturists will not tell anyone else the treatment allocation. The contacts between acupuncturists and participants should be as short as possible.
The acupuncturists will be instructed to follow standardized operating procedure:

Step 1:

The participant is piloted by research assistant to hospital bed, which was screened-off separately one-by-one. Their companions will be guided to wait outside the clinic, if any. Acupuncturist instructs the patient to lie prone on the bed, with lumbosacral and lower shin areas exposed, and tell the participant that a 30-minute treatment will be given.

Before the first session of treatment, participants will be told that they may receive either the traditional acupuncture or minimal acupuncture group, and they may not have sensation during the 30-minute retention of acupuncture needles out of body adaptation.

Step 2:

After sterilization, the acupuncturist will start to conduct administration according to treatment protocol. The acupuncture group will receive deep insertions of needles at acupoints, while the SA group will receive superficial insertions of needles at same acupoints.

Step 3:

After insertion of needles at appropriate areas, the acupuncturist will gently rotate, lift and thrust three times at each acupoint (except "BL25") to achieve the sense of sourness, distention, and heaviness (*deqi*), while no manipulation will be made in the SA group.

Step 4:

After 10 minutes, the acupuncturist will conduct the second needle manipulation in the acupuncture group, which involves light lifting, thrusting, and twirling three times at each acupoint (except "BL25"). In contrast, no manipulation will be made in the SA group.

Step 5:

After another 10 minutes, acupuncturist will conduct the third needle manipulation by light

lifting, thrusting, and twirling three times at each acupoint (except “BL25”) in the acupuncture group, while no manipulation will be made in the SA group.

Step 6:

After another 10 minutes, acupuncturist will remove the needles.

7.4 Permitted and Prohibited Concomitant Treatments

The use of medications or other therapies specific for symptoms of DLSS will be discouraged during this trial. Patients with intolerable pain will be allowed to take 200 mg dose of Celebrex (Pfizer China, Inc.) orally once a day for three consecutive days as rescue medicine with detailed record. We will compare the proportion of subjects using rescue medications between groups. Rescue medicine will be prohibited 48 hours prior to the pain and physical function assessment.

8. Subject Evaluation

8.1. Outcomes Measurements

8.1.1 Primary Outcomes

The primary outcome will be the change in the modified RMDQ score from baseline to week 6.

The RMDQ is a reliable pain-specific functional status questionnaire that is easy and simple for participants to complete [23]. The RMDQ includes 24 questions with a score range of 0–24. Notably, in this study, we will modify the response to “caused by low back or leg pain” for each question, which will be mor e suitable for participants who have sciatica [24, 25]. Disability is measured in terms of walking, standing, bending, working, sleeping, and activities of daily living. Higher scores indicate more severe symptoms, and a change in the score by 2.5 points is the minimal clinically important difference (MCID) for RMDQ scores [23]. A reduction of at least 30% and 50% reduction were additionally interpreted as minimal and substantial clinically meaningful improvement respectively [26, 27], which were adopted as secondary outcomes.

8.1.2 Secondary Outcomes

Secondary outcomes will include the following:

(1) Changes in the RMDQ score from baseline to weeks 18 and 30;

(2) The proportion of participants having at least 30% and 50% reductions in the RMDQ score from baseline to weeks 6, 18, and 30;

(3) Changes in the average pain scores for the buttocks and/or legs when walking, standing, or extending the back as measured by the NRS in the previous 1 week from baseline to weeks 6, 18, and 30.

The NRS is a concise scale for assessing pain that is completed by the participants themselves. NRS scores range from 0 to 10 with 11 grades, and higher scores indicate greater pain [28, 29]. Two scales including one for measuring buttock and/or leg pain and another for measuring low back pain will be used (participants should answer with the average score for the previous 1week). The degree of pain in the bilateral legs may be different, and data collection will be based on the degree of pain in the leg with more severe pain;

(4) The proportion of participants having at least 30% and 50% reductions from baseline in the average pain scores for the buttocks and/or legs when walking, standing, or extending the back, as measured by the NRS for the previous 1week at weeks 6, 18, and 30;

(5) Changes in the average pain score for the lower back when walking, standing, or extending the back, as measured by the NRS for the previous 1week from baseline to weeks 6, 18, and 30;

(6) Changes in the mean scores of the SSSQ for symptom severity and physical function from baseline to weeks 6, 18, and 30 and scores on the SSSQ satisfaction subscale at weeks 6, 18, and 30.

The SSSQ is a short outcome measure for symptoms and functions [30]. The SSSQ consists of 18 questions and three domains including symptom severity, physical function, and satisfaction with the degree of treatment. The scores for all three domains are calculated by taking the total score for the domain and dividing it by the number of answered questions, and if more than two items are missing, the scale scores for that domain are considered missing.

Six questions in the symptom severity domain assess pain of the back, buttocks, legs, or feet as well as pain frequency, numbness, and weakness with scores ranging from 1 to 5, while one question assesses balance with possible scores of 1, 3, and 5. Higher scores indicate worse symptoms. The physical function domain assesses walking distance and ability to walk for pleasure, shopping, and getting around the house or apartment and from the bathroom to the bedroom. This domain has five questions with scores ranging from 1 to 4, and higher scores indicate less satisfaction. The satisfaction domain has four categories (very satisfied, somewhat satisfied, somewhat dissatisfied, and very dissatisfied) with a score range of 1–4 [31, 32].

(7) The proportion of participants who are somewhat satisfied and very satisfied based on the satisfaction domain of the SSSQ at weeks 6, 18, and 30;

According to satisfaction domain of the SSSQ, patients scoring 1.5-2.5 points are regarded as somewhat satisfied with the therapy, and those scoring 1.5 points or lower are regarded as very satisfied with the therapy [33].

(8) Changes in the HADS score from baseline to weeks 6, 18, and 30.

The HADS is validated and standardized for measuring the state of anxiety and depression [34, 35]. The HADS has two subscales with 14 items (7 items each), and a total score range of 0–21 with a range of 0–3 for each item. A score of ≥ 8 indicates the presence of anxiety and/or depression.

(9) Expectancy of acupuncture

Expectancy of acupuncture will be recorded at baseline. Participants will be required to answer two questions: “In general, do you believe acupuncture is effective for treating the illness?” and “Do you think acupuncture will help to improve your symptoms of DLSS?”

(10) Blinding assessment

Patients will be asked to answer the following questions after treatment (sessions 17 or 18) within 5 min: “Do you think you have received traditional acupuncture over the past 6 weeks?” The patients can answer “yes” or “no.”

(11) Safety assessment

Adverse events (AEs) related to acupuncture include severe pain, needle breakage, fainting, local hematoma, localized infection, and post-acupuncture discomfort with symptoms such as nausea, vomiting, palpitation, dizziness, headache, anorexia, and insomnia during the treatment period. AEs irrelevant to the treatment will also be recorded in detail throughout the trial.

8.2 Evaluation Procedures

8.2.1 Schedule of Evaluation

Table 2. Enrolment, Intervention and Evaluation Schedules

	Study Period									
	Enrollment/Allocation week		**Post-allocation week**							
			Treatment week						**Follow-up**	
Timepoints	Week -1	Week 0	1	2	3	4	5	6	Week 18	Week 30
Enrollment										
Eligibility screen	×									
Informed consent	×									
MRI /CT	×									

Demographics	×									
Expectancy of acupuncture	×									
Allocation		×								
Interventions										
Acupuncture			×	×	×	×	×	×		
Sham acupuncture			×	×	×	×	×	×		
Assessments										
RMDQ	×							×	×	×
NRS	×							×	×	×
SSSQ	×							×	×	×
HADS	×							×	×	×
Blinding assessment								×		
Safety assessment	×		×	×	×	×	×	×	×	×

Abbreviations: MRI magnetic resonance imaging, CT computed tomography, RMDQ Roland-Morris Disability Questionnaire, NRS Numerical Rating Scale, SSSQ Swiss Spinal Stenosis Questionnaire, HADS Hospital Anxiety and Depression Scale

8.2.2 Baseline assessment

The demographic information and outcome assessment at baseline will be collected in Timepoint of assessment 1, which has been described in 5.2 Screening and Baseline Assessment.

8.2.3 Six-week Treatment Phase

During the 6-week treatment (weeks 1-6), Timepoint of assessment 2 will be scheduled at week 6.

Participants will complete the RMDQ, NRS, SSSQ and HADS at week 6.

Within 5 minutes after treatment (sessions 17 or 18) at the week 6, the success of blinding will be assessed by outcome assessors at hospital.

8.2.4 Twenty-four-week Follow-up Phase

During the 24-week follow-up (weeks 7-30), Timepoint of assessment 3 will be scheduled at week 18, and Timepoint of assessment 4 will be scheduled at week 30.

Participants will complete the RMDQ, NRS, SSSQ and HADS at weeks 18 and 30. We will provide a self-assessment questionnaires/scales notebook for each participant. For the results of Timepoint of assessment 3 (week 18) and Timepoint of assessment 4 (week 30), the notebook could be mailed to hospitals or submit to hospitals by participants in person.

9. Safety Assessment and Subject Withdrawal

9.1 Adverse Events

We will handle and document the adverse events (AEs) using the standard operating procedures for monitoring and reporting all AEs.

According to their potential association with the treatment, AEs will be categorized as treatment-related or non-treatment-related within 24 hours after their occurrence. Treatment-related AEs include pain, haematoma, localized infection, broken needle, fainting, nausea, headache, dizziness, insomnia, vomiting, or palpitations during or after treatment.

Serious AEs will be defined as events requiring hospitalization, causing disability or impaired ability to work, threatening life or resulting in death. Any serious AEs will be immediately reported to the principal investigator (ZL) and Medical Ethics Committee at individual clinical site and Guang'anmen Hospital within 24 hours. A research assistant will be required to record serious AEs, including information on the time of occurrence, severity, duration, measurement, management, and its outcome.

All the serious AEs and AEs will be recorded and measured by participants themselves, acupuncturists, and orthopedists through the whole trial. The participants will be followed until resolution, study completion or termination. Guang'anmen Hospital has insurance covering for harm associated with the interventions during this trial.

9.2 Subject Withdrawals

Participants may withdraw from the trial at any time at their own discretion; the investigator may also determine whether it is in the best interest of subjects to withdraw from the trial due to worsening of symptoms, or the occurrence of serious AEs.

10. Administrative Responsibilities

10.1 Institutional Review Board

For every study site, only when the trial protocol is approved by the institutional review board, the enrollment of participant will begin.

10.2 Funding

This study was supported and funded by 2019 National Administration of Traditional Chinese Medicine “Project of building evidence-based practice capacity for TCM-Project BEBPC-TCM” and Guang’anmen Hospital, China Academy of Chinese Medical Sciences. The funder will not interfere the data collection, analysis, and interpretation; nor in the finishing of the manuscript, and decision to submit the manuscript for publication.

10.3 Compliance Improvement

(1) Participants should participate in the trial voluntarily, and sign the informed consent.

(2) Research assistants should record the participants’ contact information in detail for the convenience of follow-up.

(3) Before randomization, researchers should inform the participants that all the cost related to the examination and treatment would be exempted.

(4) Each participant’s participation in the trial should be taken charge of by the same research assistant and outcome assessor throughout the trial. They will explain the contents of notebook to participants, if necessary, remind the participants of their schedule by phone or we-chat, and instruct participants to complete the notebook.

(5) For participants who have less compliance, we will still follow them up to record outcome measurements through phone or message.

10.4 Data Management

10.4.1 The Raw Data Management and Archiving

The Remote Data Capture (RDC) system will be used to perform data entry. The research assistants will fill out all the electronic Case Report Forms (eCRFs) through RDC system. Researchers will inspect the eCRF, and sign electronically for the eCRF going into effect. The eCRF and the trace of eCRF revising will be left in the Oracle database.

10.4.2 Data Entry and Storage

10.4.2.1 Database Building and Testing, Data Entry Interface

The data entry interface will be in accordance with the paper-version CRF. After preliminarily setting up the database, the entry clerks will input some analog data according to the CRF to test the database. The testing contains: (1) the agreement of the data entry interface and the paper version CRF; (2) the agreement of the exported data from the database and the analog data; (3) the agreement of the structure of the exported database and the paper-version CRF. After the testing, data administrators should revise the database and make a testing report. Then they electronically signed on the approval page of the database to indicate that the testing is completed. The electronic files of the analog CRF, noted CRF, screenshot of the data entry interface, database testing report, and the approval page of the database should be saved. If the database updates during the trial, the

electronic files mentioned above will also need to be updated.

10.4.2.2 Data Entry and Inspection

The research assistants take charge of the data entry for our trial. Before the entry, all the research assistants will accept the related training according to the data entry handbook. Researchers will inspect the database, and then sign electronically to let the data go in to effect.

10.4.3 Data Verification and Problems Solving

Researchers will verify the data through Data Verification Plan (DVP) approved by the data administrator and the statisticians. Data queries will be inputted to a data query database, and form the Data Clarification Form (DCF). After being inspected, the DCF will then be handed back to the original site, and the researchers of the site should answer the queries. Any revision of the database will be recorded through the RDC software.

10.4.4 Medical Coding

A data administrator who has the medical background is responsible for the medical coding. The coding contents include the clinical history, AEs, and combined medication use if any. The clinical history and AEs will be coded through MedDRA dictionary (Version 13.0), and the combined medication use will be coded via the Anatomical Therapeutic Chemical Classification (ATC).

10.4.5 Data Management Report

Data management report contains the aspects as followed: (1) name of the project; (2) members of the project; (3) actual first entry and finish time of every site; (4) problems and solutions during data management (if have any); (5) reconstruction of the database (if have any); (6) distribution of the participants; (7) participants who violate the trial protocol; (8) classifying plan of the statistical analysis population.

10.4.6 Data Auditing and Blinding Review

When the data checking is finished, a data auditing and blinding review meeting will be hold. In the meeting, the data administrators, statisticians, researchers, clinical inspectors, and other related members will have a discussion on the following items according to the data management report and the data lists:

- •Distribution of the participants;
- •Protocol violation;
- •Possible outlier;
- •Baseline data;
- •Outcomes;
- •Statistical analysis plan.

Participants will be classified to their suitable statistical analysis sets according to the definition in the protocol. No patient can be excluded from the analysis, unless getting the permission of the meeting participants. All the meeting participants will sign the data locking consent, and the data auditing resolution.

10.4.7 Database Locking

The database will be locked if it fulfills all the aspects as followed: All the queries have been solved, and the database has been updated; No query has been found through the data inspection; The medical coding has been completed; The plan of the participants' classification has been approved; The final draft of the statistical analysis plan (SAP) has been made, and approved by the project leader.

The statisticians and the data administrators will sign the data locking form, and then the database will be locked. The locked database will be sent to the statisticians for further statistical analysis through the data format of SAS.

10.5 Quality Control

(1) To guarantee the quality of the study, the trial protocol will be reviewed and revised by expert acupuncturists, orthopedist, and statisticians several times.

(2) A central randomization system will be adopted to avoid selection bias.

(3) Strict eligible criteria will be pre-set to restrict the research population. The diagnosis, inclusion and exclusion criteria are designed in accordance with the guidance of NASS.

(4) Trial-specific (standardized operation procedure) extensive training will be given to all the research staff participating the trial at the project launching session. Acupuncturists will be trained on how to use the central randomization system, the standardized manipulation method, and needling rituals.

Outcome assessors will be trained how to fill the case report form. Clinical Research Assistants (CRC) will be trained to use data entry system.

(5) We will provide a self-assessment questionnaires/scales notebook for each participant. Participants will be asked to complete the notebook. During 6-week treatment period, participants will bring the notebook to hospital themselves. For the outcome assessment at weeks 18 and 30, they can mail the notebook to hospital or bring the manual to hospital themselves. The data from the notebook will be the raw data for analysis, and will be checked and recorded in CRF by outcome assessors. The double-input method will be used for data entry, and all data related to patients will be stored confidentially. The statistical analysis of the data will be calculated by independent statisticians. The participants, outcome assessors, CRC and statisticians will all be unaware of the group allocation.

(6) Participation processes in the trial of the same participants should be taken charge of by the same acupuncturist, research assistant and outcome assessor throughout the trial.

(7) A 3-level monitoring system will be established to periodically assess the performance of the trial: Level 1, Inspection; Level 2, Supervision; Level 3, Audit. Inspection: The investigator of each center will designate at least one researcher who take no part in the intervention to conduct a quality review of the center; Supervision: for each center, the study organizer (Guang'anmen Hospital, China Academy of Chinese Medical Sciences) will designate at least three researchers who take no part in the intervention to monitor the quality of the studies of that center; Audit: Linkermed Pharm Technology Co., Ltd will designate at least five quality control personnel to conduct a quality audit of the research.

11. Statistical consideration

11.1 Sample Size Calculations

A sample size of 196 participants (98 in each group) was estimated to have provide at least 80% power at a 2-sided significance level of 5% to detect on a between-group difference of 2.5 points in the RMDQ score [23], assuming a standard deviation of 5.5 and a 20% dropout rate.

11.2 Statistical Analysis

Details of the pre-specified statistical analyses can be found in the Statistical Analysis Plan (SAP). Prior to database lock and before code breaking, a final version of the SAP shall be issued and approved by the study statistician, and the principal investigator. The SAP will define all “pre-specified, planned analyses” and provide the general specifications for the analysis of the data to be collected and presented in the Clinical Study Report.

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Appendix 1 Patient Informed Consent

Dear participants:

If your doctor thinks you have degenerative lumbar spinal stenosis (DLSS), we invite you to participate in this study aiming to evaluate the effectiveness and safety of acupuncture for management of DLSS.

Before you decide to participate in the study, please read the following information carefully. It is helpful for you to know this study, understand why the study is performed, the study procedures, the duration and benefits of the study, risks and potential discomforts during and after study participation.

If you like, you can also discuss this study with your relatives and friends, or consult doctors for explanation and help to make the decision.

I. Introduction

DLSS is a common cause of gluteal and lower extremity pain and more likely to affect women and elderly people aged 60-70 years. In accordance with the guidelines of the North American Spine Society, treatment options comprise surgical therapy, epidural steroid injections and physical therapy, and transcutaneous electrical stimulation. However, according to some studies, the long-term efficacy of surgery is not superior to that of non-surgical therapy. Previous studies suggest that acupuncture may be a potential treatment for DLSS.

In this study, a randomized controlled trial design will be used and we aim to evaluate the effectiveness and safety of acupuncture for relieving symptoms of DLSS. This study will be carried out simultaneously in 5 hospitals all over China, and we expect a total number of 196 participants for voluntary participation.

II. Inclusion and exclusion criteria

Participants will be eligible if they:

(1) Meet the requirements for a clinical diagnosis of DLSS combined with an MRI- or CT-based radiological diagnosis of central sagittal diameter stenosis of the lumbar spinal canal;

(2) Have neurogenic intermittent claudication characterized by progressive pain of the buttocks and/or legs when standing or walking or with extension of the back, which are relieved upon sitting, lying down, or bending forward [20]; they always walk in flexion or hunchback posture;

(3) Have pain of an intensity ≥4 in the buttocks and/or legs when walking, standing, or extending the back, as measured using the Numerical Rating Scale (NRS);

(4) Have pain in the buttock and/or leg that is more severe than their pain in the lower back;

(5) Have a Roland-Morris Disability Questionnaire (RMDQ) score of at least 7;

(6) MRI (mainly) or CT scan showed the anterior posterior diameter of the canal was ≤ 12 mm;

(7) Are aged 50-80 years;

(8) Have provided signed consent and exhibit willingness to participate in the trial.

Patients will be excluded if they have:

(1) Congenital stenosis of the vertebral canal, indications of surgery for DLSS (e.g., segmental muscular atrophy, bowel and bladder disturbances), spinal instability requiring surgery, lumbar tuberculosis, lumbar metastatic carcinoma, vascular claudication, or vertebral body/vertebral stenosis segment compression fracture;

(2) Severe vascular, pulmonary, or coronary artery disease with limited lower extremities motility;

(3) Clinical comorbidities that could interfere with the collection of data related to pain and walking function such as fibromyalgia, chronic widespread pain, amputation, stroke, Parkinson's disease, spinal cord injury, and dementia;

(4) Cognitive impairment, such that they are unable to understand the content of the assessment scales or provide accurate data;

(5) A history of lumbar surgery;

(6) Plans to become pregnant within 12 months or are already pregnant;

(7) Received acupuncture treatments for DLSS within the previous 30days;

(8) Neurogenic intermittent claudication mainly manifesting as numbness, weakness, or paresthesia of the lower extremities instead of pain.

III. What do you do next, if you decide to participate?

1. Before your enrollment in the study, your medical history will be collected and you will receive a series of examinations to determine whether you are eligible to participate in the study, including physical examination, magnetic resonance imaging (MRI) or computed tomography (CT) if the scan is longer than 1 year. You will also need to complete a series of questionnaires to assess the severity of the disease and the influence on quality of life.

2. If the results of the above screening examinations meet the inclusion criteria and you are willing to participate in this study, you will be invited to continue study participation in the following steps:

(1) Based on the random number generated from the computer, the doctor will assign you to either the traditional acupuncture or minimal acupuncture group. Participants in the traditional acupuncture group will receive deep needling on the bilateral Shenshu (BL23), "Dachangshu (BL25)", Weizhong (BL40), Chengshan (BL57), and Taixi (KI3) for 30 min; participants in the minimal acupuncture group will receive minimally invasive, superficial needle insertion of 2-3mm on the same points.

(2) In the study, Hwato brand disposable needles (Suzhou Medical Appliance, Jiangsu, China, Jiangsu Food, Drug, and Medical Appliance Administration production approval No.: 20010020, Registration No:20162200970) will be used.

(3) The duration of this study is 31 weeks in total for a patient including 1-week baseline assessment, 6-week treatment, and 24-week follow up. Frequency and duration of acupuncture: 3 sessions per week in weeks 1-6. The participants will receive 18 sessions of treatment in total.

(4) During the study period, you need to complete the questionnaires faithfully.

3. Other requirements for your cooperation

As a participant of this study, you will have some relevant responsibilities, such as adherence to the schedule for examination, treatment, and clinical follow-up. Additionally, you are also responsible for reporting any changes in your physical and mental status to your doctor during the study process regardless of whether you think these changes are related to the study or not. You should follow the scheduled appointments with the doctor to come to the hospital for treatment. Your follow-up is very important because the doctor will determine whether the treatment that you are receiving really works and their safety profile.

During the study, you are not allowed to use other treatments for DLSS. However, for intolerable symptoms, medication use such as Celecoxib capsules (Celebrex) is allowed, as long as it is recorded accordingly, including the name and the dosage of the medication use.

IV. Potential benefits of study participation

You may benefit from this study. The benefits may include improvement of symptoms, even by minimal acupuncture. The study may also help doctors and researchers to further evaluate the efficacy of acupuncture for DLSS. The information will be beneficial in the management of other patients with a similar condition in the future. If you decide to participate in the study, you will get relevant physical and biochemical examination as well the study intervention for free during the study period.

V. Potential side effects, risks, discomforts, and inconveniences

The doctors will make every effort to prevent and treat any side effects brought on by this study. During treatment, you may feel soreness, numbness, heavy, distension sensation, etc., which are normal reactions to acupuncture. Acupuncture treatment may have some adverse effects, but it is rare and mild. You may feel fainting due to your individual physique or emotional stress when receive acupuncture needling. Your symptoms should be relieved after the cessation of acupuncture treatment and rest. Localized bleeding, hematoma, and other phenomena may occur after acupuncture treatment, and these phenomena should disappear after applying local pressure. If infection occurs in the needle site, your doctor will handle it timely. With the treatment following the study protocol in the study, if you experience adverse reactions and events related to acupuncture treatment, please feel free to call your doctor for help. The doctor will provide you timely treatment. If injuries have been confirmed and are caused by adverse reactions and events of the study, the study group will deal with them appropriately in accordance with relevant provisions. If you experience any discomfort or new change of your symptoms, or any other unforeseen circumstances during study period, regardless of whether these events are relevant with treatment of the study or not, you shall promptly notify your doctor, and he /she will evaluate the condition and give you appropriate medical treatment.

VI. Payments/compensation for participation

If you participate in the study, during the study, you will get relevant physical and biochemical examination and acupuncture treatment for free. If adverse events occur during the study, they will be managed accordingly by medical experts who will also identify whether they are related to the study or not. The treatment and examination required for your concomitant diseases nonrelated to the study will not be free of charge.

VII. Confidentiality of personal information

All the information related to your participation in this study will be kept confidential by the institute where your participation takes place. Only the institutes responsible for the study, clinical research institutes, and ethics committees may have access to your medical records. Your name will not appear in any publication or report related to this study. We will make every effort to protect the privacy of your personal medical information as per legal requirements and laws.

VIII. How to acquire extra information?

You can ask any questions about the study at any time and will get answers timely. If we notice any new information that may affect your willingness and decision to continue participating in the study, the doctor will keep you informed.

IX. Can you voluntarily choose to participate in or withdraw from the study?

Whether to participate in this study or not entirely depends on your desire. You can refuse to participate in the study, or withdraw from the study at any time during the study, which will not affect the relationship between you and your doctor and will not affect your medical interests or interests in other areas. For the consideration of your best interests, doctors or researchers may

terminate your participation in this study at any time. If you withdraw from the study for any reason, you may be asked for information related of acupuncture treatment or the use of other medications during your participation of the study. If the doctor considers it necessary, you may also be asked to have some laboratory tests and physical examinations performed.

X. What you need to do now?

Decide whether to participate in this study or not. Before you make the decision to participate in the study, please ask your doctor if you have any concerns.

Thank you for reading the above information. If you decide to participate in this study, please tell your doctor, he / she will help you make arrangement for the study.

Please keep this document for your own record.

Informed Consent: Signature Page

Study title: Efficacy of acupuncture for treatment of intermittent claudication in patients with degenerative lumbar spinal stenosis: protocol for a randomized controlled trial

Organizer of this study: Guang'anmen Hospital, China Academy of Chinese Medical Sciences

Collaborative institute:

Statement of agreement:

I have read the above information about this study and have the opportunity to discuss this study with my doctor and ask questions. All my questions were answered satisfactorily. I understand the potential risks and benefits from participation in this study. I understand the participation of the study is voluntary and I confirm that I was given sufficient time for consideration of study participation. I confirm that I understand that:

I can always ask the doctor for additional/more information.

I can withdraw from the study at any time without discrimination or retaliation and my medical treatment and interests will not be affected.

I understand that if I withdraw from the study, I will tell the doctor the changes of my disease condition and complete the relevant physical and biochemical examinations if needed, which will be very helpful for the whole study.

If I need to take any other medications due to the changes of my medical condition, I will seek medical advice from the doctor beforehand or afterwards tell the doctor truthfully.

I agree to allow the research institute, collaborative institutes, and ethics committees to inspect the data relevant to my study participation.

I will receive a signed and dated copy of the informed consent form.

Finally, I decide and agree to participate in this study and ensure the adherence to doctor's orders to the best I can.

Signature of patient: Year month day

Telephone:

I confirm that I have explained this study in detail to the patient, including patient's rights as well as the potential benefits and risks, and have given the patient a signed copy of the informed consent form.

Signature of doctor: Year month day

Office phone number of doctor:

Appendix 2 Outcome Assessment Tools

List of the outcome assessment tools:
Modified Roland-Morris Disability Questionnaire (RMDQ)
Numerical Rating Scale (NRS)
Swiss Spinal Stenosis Questionnaire (SSSQ)
Hospital Anxiety and Depression Scale (HADS)
Expectation Assessment

Modified Roland-Morris Disability Questionnaire (RMDQ)

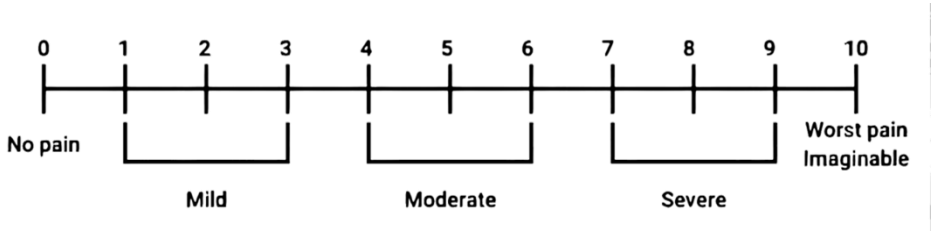
When your back or leg hurts, you may find it difficult to do some things you normally do.
This list contains sentences that people have used to describe themselves when they have back or leg pain. When you read them, you may find that some stand out because they describe you today. As you read the list, think of yourself today. When you read a sentence that describes you today, put a tick against it. If the sentence does not describe you, then leave the space blank and go on to the next one. Remember, only tick the sentence if you are sure it describes you today.

1. I stay at home most of the time because of my back problem or leg pain.
2. I change position frequently to try and get my back or leg comfortable.
3. I walk more slowly than usual because of my back problem or leg pain.
4. Because of my back problem or leg pain, I am not doing any of the jobs that I usually do around the house.
5. Because of my back problem or leg pain, I use a handrail to get upstairs.
6. Because of my back or leg, I lie down to rest more often.
7. Because of my back problem or leg pain, I have to hold on to something to get out of an easy chair.
8. Because of my back problem or leg pain, I try to get other people to do things for me.
9. I get dressed more slowly then usual because of my back problem or leg pain.
10. I only stand for short periods of time because of my back problem or leg pain.
11. Because of my back problem or leg pain, I try not to bend or kneel down.
12. I find it difficult to get out of a chair because of my back problem or leg pain.
13. My back or leg is painful almost all the time.
14. I find it difficult to turn over in bed because of my back problem or leg pain.
15. My appetite is not very good because of my back problem or leg pain.
16. I have trouble putting on my socks (or stockings) because of the pain in my back or leg.
17. I only walk short distances because of my back or leg back.
18. I sleep less well because of my back or leg problem.
19. Because of my back or leg pain, I get dressed with help from someone else.
20. I sit down for most of the day because of my back problem or leg pain.
21. I avoid heavy jobs around the house because of my back problem or leg pain.
22. Because of my back or leg pain, I am more irritable and bad tempered with people than usual.
23. Because of my back or leg pain, I go upstairs more slowly than usual.
24. I stay in bed most of the time because of my back or leg.

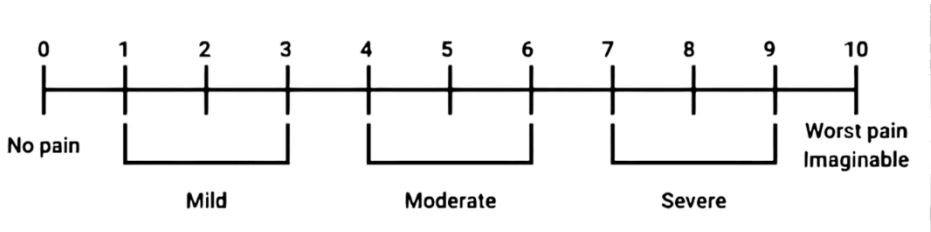
The score is the total number of items checked—i.e., from a minimum of 0 to a maximum of 24.

buttocks and/or legs or back average pain measured by Numerical Rating Scale (NRS)

The average pain scores for the buttocks and/or legs when walking, standing, or extending the back in the previous 1 week
(The degree of pain in the bilateral legs may be different, and data collection will be based on the degree of pain in the leg with more severe pain)



The average pain scores for the lower back when walking, standing, or extending the back in the previous 1 week



Swiss Spinal Stenosis Questionnaire (SSSQ)

Table 1. Component Items of the Symptom Severity Scale with Preoperative Responses

In the last month, how would you describe:	
1. The pain you have had on average including pain in your back, buttocks and pain that goes down the legs?	□1 None
	□2 Mild
	□3 Moderate
	□4 Severe
	□5 Very severe
2. How often have you had back, buttock, or leg pain?	□1 Less than once a week
	□2 At least once a week
	□3 Everyday, for at least a few minutes
	□4 Everyday, for most of the day
	□5 Every minute of the day
3. The pain in your back or buttocks?	□1 None
	□2 Mild
	□3 Moderate
	□4 Severe
	□5 Very severe
4. The pain in your legs or feet?	□1 None
	□2 Mild
	□3 Moderate
	□4 Severe
	□5 Very severe
5. Numbness or tingling in your legs or feet?	□1 None
	□2 Mild
	□3 Moderate
	□4 Severe
	□5 Very severe
6. Weakness in your legs or feet?	□1 None
	□2 Mild
	□3 Moderate
	□4 Severe
	□5 Very severe
7. Problems with your balance?	□1 No, I've had no problems with balance
	□3 Yes, sometimes I feel my balance
	□5 Yes, often I feel my balance is off, or that I am not sure-footed

Table 2. Component Items of the Physical Function Scale (Before Surgery)

In the last month, on a typical day:	
8. How far have you been able to walk?	□1 Over 2 miles

	□2 Over 2 blocks, but less than 2 miles
	□3 Over 50 feet, but less than 2 blocks
	□4 Less than 50 feet
9. How you taken walks outdoors or in malls for pleasure?	□1 Yes, comfortably
	□2 Yes, but sometimes with pain
	□3 Yes, but always with pain
	□4 No
10. Have you been shopping for groceries or other items?	□1 Yes, comfortably
	□2 Yes, but sometimes with pain
	□3 Yes, but always with pain
	□4 No
11. Have you walked around the different rooms in your house or apartment?	□1 Yes, comfortably
	□2 Yes, but sometimes with pain
	□3 Yes, but always with pain
	□4 No
12. Have you walked from your bedroom to the bathroom?	□1 Yes, comfortably
	□2 Yes, but sometimes with pain
	□3 Yes, but always with pain
	□4 No

Table 3. Component Items of the Satisfaction Scale

How satisfied are you with:			
13. The overall result of back treatment?			
□ Very satisfied	□ Somewhat satisfied	□ Somewhat dissatisfied	□ Very dissatisfied
14. Relief of pain following the treatment?			
□ Very satisfied	□ Somewhat satisfied	□ Somewhat dissatisfied	□ Very dissatisfied
15. Your ability to walk following the treatment?			
□ Very satisfied	□ Somewhat satisfied	□ Somewhat dissatisfied	□ Very dissatisfied
16. Your ability to do housework, yard work, or job following the treatment?			
□ Very satisfied	□ Somewhat satisfied	□ Somewhat dissatisfied	□ Very dissatisfied
17. Your strength in the things, legs, and feet?			
□ Very satisfied	□ Somewhat satisfied	□ Somewhat dissatisfied	□ Very dissatisfied
18. Your balance, or steadiness on your feet?			
□ Very satisfied	□ Somewhat satisfied	□ Somewhat dissatisfied	□ Very dissatisfied

Hospital Anxiety and Depression Scale (HADS)

Tick the box beside the reply that is closest to how you have been feeling in the past week. Don't take too long over you replies: your immediate is best.

1. I feel tense or "wound up":
□3 Most of the time
□2 A lot of the time
□1 From time to time, occasionally
□0 Not at all

2. I still enjoy the things I used to enjoy:
□0 Definitely as much
□1 Not quite so much
□2 Only a little
□3 Hardly at all

3. I get a sort of frightened feeling as if something awful is about to happen:
□3 Very definitely and quite badly
□2 Yes, but not too badly
□1 A little, but it doesn't worry me
□0 Not at all

4. I can laugh and see the funny side of things:
□0 As much as I always could
□1 Not quite so much now
□2 Definitely not so much now
□3 Not at all

5. Worrying thoughts go through my mind:
□3 A great deal of the time
□2 A lot of the time
□1 From time to time, but not too often
□0 Only occasionally

6. I feel cheerful:
□3 Not at all
□2 Not often
□1 Sometimes
□0 Most of the time

7. I can sit at ease and feel relaxed:
□0 Definitely
□1 Usually
□2 Not Often
□3 Not at all

8. I feel as if I am slowed down:
□3 Nearly all the time
□2 Very often
□1 Sometimes
□0 Not at all

9. I get a sort of frightened feeling like 'butterflies' in the stomach:
□0 Not at all
□1 Occasionally
□2 Quite Often
□3 Very Often

10. I have lost interest in my appearance:
□3 Definitely
□2 I don't take as much care as I should
□1 I may not take quite as much care
□0 I take just as much care as ever

11. I feel restless as I have to be on the move:
□3 Very much indeed
□2 Quite a lot
□1 Not very much
□0 Not at all

12. I look forward with enjoyment to things:
□0 As much as I ever did
□1 Rather less than I used to
□2 Definitely less than I used to
□3 Hardly at all

13. I get sudden feelings of panic:
□3 Very often indeed
□2 Quite often
□1 Not very often
□0 Not at all

14. I can enjoy a good book or radio or TV program:
□0 Often
□1 Sometimes
□2 Not often
□3 Very seldom

Expectation Assessment

In general, is acupuncture effective for controlling the illness?
□ Yes
□ No
□ Unclear
Do you think acupuncture will be helpful to improve your DLSS symptoms
□ Yes
□ No
□ Unclear

Efficacy of acupuncture for treatment of intermittent claudication in patients with degenerative lumbar spinal stenosis

Statistical Analysis Plan (SAP)

NCT number: NCT03784729

February 25, 2019

Content

1. Introduction

Degenerative lumbar spinal stenosis (DLSS) is a condition involving narrowing of the space for the sagittal diameter of the spinal canal or nerve root canal for the spinal nerve or cauda equina secondary to degenerative changes [1-3]. DLSS is a common cause of gluteal and lower extremity pain and more likely to affect women and elderly people aged 60–70 years [4]. Because imaging evidence is not necessarily related to clinical symptoms, there are no specific epidemiological data for DLSS [5, 6]. According to the results of magnetic resonance imaging (MRI), 30–90% of asymptomatic adults may have spinal abnormalities including disc herniation, disc degeneration, or spinal stenosis [7]. DLSS is the most common type of spinal stenosis [1, 8]. The early symptoms of DLSS are soreness and pain in the low back, gluteal region, and posterior region of the thighs, which can be relieved after resting or changing posture. As patients with DLSS experience gradually aggravated symptoms, they may have neurogenic claudication with hypoesthesia and numbness in the lateral lower legs and feet; additionally, some patients may have bowel and bladder disturbances [9, 10]. DLSS patients have a poor quality of life, especially elderly patients [11]. In accordance with the guidelines of the North American Spine Society, treatment options comprise surgical therapy, epidural steroid injections and physical therapy, and transcutaneous electrical stimulation. According to some studies, the long-term efficacy of surgery is not superior to that of non-surgical therapy [12-15]. More studies are required to explore the efficacy of non-surgical therapy [16]. According to a systematic review [17] and recent studies [18, 19], acupuncture may improve the symptoms of patients and thus their quality of life; however, there is a lack of placebo-controlled and large-sample sized studies. More studies with a sufficient sample size are needed to provide evidence of the efficacy of acupuncture for treating DLSS.

2. Study Objective

The aim of this study is to assess the effects and safety of acupuncture for relieving predominantly neurogenic claudication pain in patients with central DLSS.

3. Design

3.1 Overview

This is a multicenter, participants-blinded, parallel-group, randomized controlled study conducted in China.

The participants will be recruited in 5 clinical sites, which are Guang'anmen Hospital, China Academy of Chinese Medical Sciences; Shaanxi Provincial Hospital of Traditional Chinese Medicine; Guangdong Provincial Hospital of Traditional Chinese Medicine; The First Hospital of Hunan University of Chinese Medicine; The Third Affiliated People's Hospital of Fujian University of Traditional Chinese Medicine. The study design and organization will be responsible by Guang'anmen Hospital, China Academy of Chinese Medical Sciences. A data coordination center will be established at Linkermed Pharm Technology Co., Ltd (Beijing, China) to monitor data management.

3.2 Eligibility criteria

3.2.1 Inclusion Criteria

(1) Meet the requirements for a clinical diagnosis of DLSS combined with an MRI- or CT-based radiological diagnosis of central sagittal diameter stenosis of the lumbar spinal canal;

(2) Have neurogenic intermittent claudication characterized by progressive pain of the buttocks and/or legs when standing or walking or with extension of the back, which are relieved upon sitting, lying down, or bending forward [20]; they always walk in flexion or hunchback posture;

(3) Have pain of an intensity ≥4 in the buttocks and/or legs when walking, standing, or extending the back, as measured using the Numerical Rating Scale (NRS);

(4) Have pain in the buttock and/or leg that is more severe than their pain in the lower back;

(5) Have a Roland-Morris Disability Questionnaire (RMDQ) score of at least 7;

(6) MRI (mainly) or CT scan showed the anterior posterior diameter of the canal was ≤ 12 mm;

(7) Are aged 50-80 years;

(8) Have provided signed consent and exhibit willingness to participate in the trial.

3.2.2 Exclusion Criteria

(1) Congenital stenosis of the vertebral canal, indications of surgery for DLSS (e.g., segmental muscular atrophy, bowel and bladder disturbances), spinal instability requiring surgery, lumbar tuberculosis, lumbar metastatic carcinoma, vascular claudication, or vertebral body/vertebral stenosis segment compression fracture;

(2) Severe vascular, pulmonary, or coronary artery disease with limited lower extremities motility;

(3) Clinical comorbidities that could interfere with the collection of data related to pain and walking function such as fibromyalgia, chronic widespread pain, amputation, stroke, Parkinson's disease, spinal cord injury, and dementia;

(4) Cognitive impairment, such that they are unable to understand the content of the assessment scales or provide accurate data;

(5) A history of lumbar surgery;

(6) Plans to become pregnant within 12 months or are already pregnant;

(7) Received acupuncture treatments for DLSS within the previous 30days;

(8) Neurogenic intermittent claudication mainly manifesting as numbness, weakness, or paresthesia of the lower extremities instead of pain.

4. Schedule of Evaluation

	Study Period									
	Enrollment/Allocation week		**Post-allocation week**							
			Treatment week						**Follow-up**	
Timepoints	Week -1	Week 0	1	2	3	4	5	6	Week 18	Week 30
Enrollment										
Eligibility screen	×									
Informed consent	×									
MRI/CT	×									
Demographics	×									
Expectancy of acupuncture	×									
Allocation		×								
Interventions										
Acupuncture			×	×	×	×	×	×		
Sham acupuncture			×	×	×	×	×	×		
Assessments										
RMDQ	×							×	×	×
NRS	×							×	×	×
SSSQ	×							×	×	×
HADS	×							×	×	×
Blinding assessment								×		
Safety assessment			×	×	×	×	×	×	×	×

Table 1. Enrolment, Intervention and Evaluation Schedules

Abbreviations: MRI magnetic resonance imaging, CT computed tomography, RMDQ Roland-Morris Disability Questionnaire, NRS Numerical Rating Scale, SSSQ Swiss Spinal Stenosis Questionnaire, HADS Hospital Anxiety and Depression Scale

5. Efficacy and Safety outcomes

5.1 Efficacy outcomes

5.1.1 Primary Outcome

The primary outcome will be the change in the modified RMDQ score from baseline to week 6.

The RMDQ is a reliable pain-specific functional status questionnaire that is easy and simple for participants to complete [23]. The RMDQ includes 24 questions with a score range of 0–24. Notably, in this study, we will modify the response to "caused by low back or leg pain" for each question, which will be mor e suitable for participants who have sciatica [24, 25]. Disability is measured in terms of walking, standing, bending, working, sleeping, and activities of daily living. Higher scores indicate more severe symptoms, and a change in the score by 2.5 points is the minimal clinically important difference (MCID) for RMDQ scores [23]. A reduction of at least 30% and 50% reduction were additionally interpreted as minimal and substantial clinically meaningful improvement respectively [26, 27], which were adopted as secondary outcomes.

5.1.2 Secondary Outcomes

Secondary outcomes will include the following:

(1) Changes in the RMDQ score from baseline to weeks 18 and 30;

(2) The proportion of participants having at least 30% and 50% reductions in the RMDQ score from baseline to weeks 6, 18, and 30;

(3) Changes in the average pain scores for the buttocks and/or legs when walking, standing, or extending the back as measured by the NRS in the previous 1 week from baseline to weeks 6, 18, and 30.

The NRS is a concise scale for assessing pain that is completed by the participants themselves. NRS scores range from 0 to 10 with 11 grades, and higher scores indicate greater pain [28, 29]. Two scales including one for measuring buttock and/or leg pain and another for measuring low back pain will be used (participants should answer with the average score for the previous 1week). The degree of pain in the bilateral legs may be different, and data collection will be based on the degree of pain in the leg with more severe pain;

(4) The proportion of participants having at least 30% and 50% reductions from baseline in the average pain scores for the buttocks and/or legs when walking, standing, or extending the back, as measured by the NRS for the previous 1week at weeks 6, 18, and 30;

(5) Changes in the average pain score for the lower back when walking, standing, or extending the back, as measured by the NRS for the previous 1week from baseline to weeks 6, 18, and 30;

(6) Changes in the mean scores of the SSSQ for symptom severity and physical function from baseline to weeks 6, 18, and 30 and scores on the SSSQ satisfaction subscale at weeks 6, 18, and 30.

The SSSQ is a short outcome measure for symptoms and functions [30]. The SSSQ consists of 18 questions and three domains including symptom severity, physical function, and satisfaction with the degree of treatment. The scores for all three domains are calculated by taking the total score for the domain and dividing it by the number of answered questions, and if more than two items are missing, the scale scores for that domain are considered missing.

Six questions in the symptom severity domain assess pain of the back, buttocks, legs, or feet

as well as pain frequency, numbness, and weakness with scores ranging from 1 to 5, while one question assesses balance with possible scores of 1, 3, and 5. Higher scores indicate worse symptoms. The physical function domain assesses walking distance and ability to walk for pleasure, shopping, and getting around the house or apartment and from the bathroom to the bedroom. This domain has five questions with scores ranging from 1 to 4, and higher scores indicate less satisfaction. The satisfaction domain has four categories (very satisfied, somewhat satisfied, somewhat dissatisfied, and very dissatisfied) with a score range of 1–4 [31, 32].

(7) The proportion of participants who are somewhat satisfied and very satisfied based on the satisfaction domain of the SSSQ at weeks 6, 18, and 30;

According to satisfaction domain of the SSSQ, patients scoring 1.5-2.5 points are regarded as somewhat satisfied with the therapy, and those scoring 1.5 points or lower are regarded as very satisfied with the therapy [33].

(8) Changes in the HADS score from baseline to weeks 6, 18, and 30.

The HADS is validated and standardized for measuring the state of anxiety and depression [34, 35]. The HADS has two subscales with 14 items (7 items each), and a total score range of 0–21 with a range of 0–3 for each item. A score of ≥ 8 indicates the presence of anxiety and/or depression.

(9) Expectancy of acupuncture

Expectancy of acupuncture will be recorded at baseline. Participants will be required to answer two questions: “In general, do you believe acupuncture is effective for treating the illness?” and “Do you think acupuncture will help to improve your symptoms of DLSS?”

(10) Blinding assessment

Patients will be asked to answer the following questions after treatment (sessions 17 or 18) within 5 min: “Do you think you have received traditional acupuncture over the past 6 weeks?” The patients can answer “yes” or “no.”

(11) Safety assessment

Adverse events (AEs) related to acupuncture include severe pain, needle breakage, fainting, local hematoma, localized infection, and post-acupuncture discomfort with symptoms such as nausea, vomiting, palpitation, dizziness, headache, anorexia, and insomnia during the treatment period. AEs irrelevant to the treatment will also be recorded in detail throughout the trial.

5.2 Safety outcomes

According to their potential association with the treatment, AEs will be categorized as treatment-related or non-treatment-related within 24 hours after their occurrence. Treatment-related adverse events include pain, haematoma, localized infection, broken needle, fainting, nausea, headache, dizziness, insomnia, vomiting, or palpitations during or after treatment.

Serious AEs will be defined as events requiring hospitalization, causing disability or impaired ability to work, threatening life or resulting in death.

All the AEs and serious AEs, whether related to acupuncture or not, will be reported and documented.

6. Statistical Considerations

6.1 Study Hypothesis

The null hypothesis is that the change from baseline in the modified RMDQ score at week 6 would be the same for acupuncture and SA, and the alternative hypothesis was that the change would differ.

6.2 Statistical Analysis Set

The efficacy analyses will be done on the intention-to-treat (ITT) population, which will include all participants who will be randomized according to randomized treatment assignment. The safety analysis will be done on the safety population, which will include the ITT participants who received any treatment.

6.3 Statistical Analyses

6.3.1 The general principle

Summary Statistics

Summary tables (descriptive statistics and/or frequency tables) will be provided for all variables at different endpoints. For continuous variables, means and standard deviations will be presented, unless the variable has a skewed distribution, in which case medians, 25th and 75th percentiles will be presented. For categorical variables, the number and percentage of participants within each category will be presented. For each variable (continuous or categorical), the number of missing values will be reported.

Statistical Comparisons Between Groups

Continuous variables will be compared using a two-sample t-test or Wilcoxon rank-sum test if data show serious deviations from a normal distribution. Categorical data or ordinal data will be compared using a Chi-square test, Fisher's exact test or Wilcoxon rank-sum test, as appropriate.

For the analyses of the primary and secondary outcomes, estimated treatment differences and associated 95% two-sided confidence intervals will be presented.

Multicenter study

The study will be conducted by multiple investigators in 5 centers. The randomization sequence will be generated in varying blocking sizes and stratified by center. To estimate the overall variability of the center effects, we will perform a sensitivity analysis for the primary outcome.

Multiple Comparisons

For the analyses of the secondary and safety outcomes, no adjustment for multiple comparisons will be made.

Analysis Software

For all statistical analyses, SAS 9.4 software will be used. All hypothesis testing will be carried out at the 5% (2-sided) significance level.

6.3.2 Demographics and Baseline Characteristics

All data recorded at baseline will be summarized by group. Comparisons between groups will be performed using the methodology described in section 6.3.1. Summaries will be presented for the ITT set in both groups.

6.3.3 Analysis for Primary Outcome

The primary analysis will be conducted a mixed effects model for repeated measures (MMRM). In this model, the observed change from baseline score at each scheduled post-baseline visit will be the dependent variable. The model will include the baseline RMDQ score as a fixed effect, with categorical factors for treatment group (acupuncture and SA), visit and treatment × visit interactions. The interactions will remain in the model regardless of significance. Treatment group comparisons at each visit will be estimated by differences between least squares (LS) means from the treatment × visit interaction, with accompanying *P*-values and 95% CIs. An unstructured covariance pattern will be used to estimate the variance–covariance of the within-subject repeated measures. Parameters will be estimated using maximum likelihood with the Newton-Raphson algorithm and using the Kenward–Roger method for calculating the denominator degrees of freedom.

Sensitivity Analyses for the Primary Outcome

Multiple imputation will be used to impute missing values under the missing-at random assumption (MAR). Specifically, 100 imputed data sets will be generated using the fully conditional specification method or regression method with the number of iterations set to 10 for the following variables: group, baseline value and dependent variable. After multiple imputation, each of the hundred multiple imputation datasets will be analyzed using the MMRM model. The overall estimates will be calculated using Rubin's rules. The multiple imputation procedure (PROC MI) in SAS, version 9.4 will be used and *P*-value <0.05 will be considered statistically significant. To address potential center differences, we will incorporate site as either a fixed or random effect in the MMRM model.

6.3.4 Analyses for Secondary Outcome

Efficacy analyses for all secondary outcomes will be performed in the ITT population, without imputation of missing data.

The same approach for the primary outcome will be used in other continuous outcomes such as SSSQ for symptom severity, physical function. Categorical data will be compared between groups using a generalized linear model with a binomial distribution and identity link that will include the same covariate as the MMRM model. In addition to the proportion of participants who were somewhat satisfied and very satisfied based on the satisfaction domain of the SSSQ, we will be analysis use the generalized linear model with the same covariate as the MMRM model. Patients' expectations of acupuncture for general disease and for DLSS, blinding, adherence data will present for descriptive purposes only.

6.3.5 Safety Analyses

All AEs and serious AEs will be listed. AEs include the acupuncture-related AEs and other AEs. AE data will be provided for descriptive purposes only.

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