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The long-term effect of 4 weeks versus 8 weeks of acupuncture for knee osteoarthritis: protocol for a randomized controlled trial

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Manuscripts

The long-term effect of 4 weeks versus 8 weeks of acupuncture for knee osteoarthritis: protocol for a randomized controlled trial

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Abstract

Introduction Knee osteoarthritis represents the prevalent and incapacitating disease. Acupuncture, a widely used clinical treatment for knee osteoarthritis, has been shown to ameliorate pain and enhance joint function in affected individuals. However, there is a lack of evidence comparing different courses of acupuncture for knee osteoarthritis. In this trial, we will assess the effect of 4 weeks versus 8 weeks of acupuncture in patients with knee osteoarthritis.

Methods and analysis The protocol is a pragmatic, parallel, two-armed randomized controlled trial, with data analyst and assessor being blinded. 148 eligible patients with knee osteoarthritis will be randomly allocated in a 1:1 radio to receive 4-week or 8-week acupuncture. Electro-acupuncture will be administered 3 times per week for 4 or 8 weeks, respectively. Patients with knee osteoarthritis in both groups will be followed up to 26 weeks. The primary outcome is the response rate at week 26, and secondary outcomes include knee-joint pain, knee-joint function, knee-joint stiffness, quality of life, patient global assessment, the Osteoarthritis Research Society International response rate and rescue medicine. A cost-effectiveness analysis will be carried out over 26 weeks.

Ethics and dissemination The study has obtained ethics approval from the Research Ethical Committee of Beijing University of Chinese Medicine (No.2023BZYL0506). The study findings will be disseminated through presentation in a high-impact medical journal, with online access. Additionally, we plan to present them at select conferences and scientific meetings.

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Trial registration The trial has been registered in the Chinese Clinical Trials Registry (ChiCTR2300073383. Register date: July 10, 2023, *https://www.chictr.org.cn/showproj.html?proj=199310*).

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Strengths and limitations of this study

1. The research will provide strong clinical evidence of different acupuncture treatment courses on their effect.
2. Strict standardization of endpoints and objective criteria, long-term follow-up, rigorous quality control, and evaluation of patients' expectations for acupuncture are aimed at reducing the risk of bias.
3. The nature of the intervention precludes the possibility of blinding both acupuncturists and patients, which may bring bias.
4. Only patients with KL II or III will be included in this trial and results of the research will not be generalized to patients with KL IV.
5. The trial only compared 2 common treatment courses of acupuncture, 4 weeks and 8 weeks, without any comparison to other courses.

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Background

Osteoarthritis, a degenerative joint disease, is a prevalent affliction among adults globally, with the knee joint being the most commonly affected[1 2]. Estimates published in 2020 suggest that 300 million people worldwide are affected by hip and knee osteoarthritis (KOA)[3]. KOA is characterized by pain and functional limitations, which impairs patients' quality of life seriously[2 4], with age, gender, obesity, excessive physical activities and previous knee trauma being some of the associated risk factors[1 5]. Of note, female patients are more likely to suffer from KOA compared to males[1 6]. And the incidence of KOA increases with age, making it a major contributor to disability in elderly population[1 6]. The annual sick leave costs due to knee and hip osteoarthritis are about €40 million for the Dutch workforce, and KOA costs approximately twice as much as hip osteoarthritis[7]. KOA reduces the employability of patients and raises the cost of healthcare, which places a heavy financial burden on individuals and society.

Acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs) are strongly recommended for KOA patients in the guideline[8]. Nonetheless, using acetaminophen alone is not much of a role[9]. Taking into consideration the potential gastrointestinal and cardiovascular side effect, NSAIDs should be used for shortest duration possible[10]. Intra-articular corticosteroid injections may be an effective management strategy for KOA patients, but long-term usage increases the risk of joint deterioration[11 12]. Opioid has limited benefits for KOA and a elevated risk of the gastrointestinal adverse event

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or somnolence[13-16]. Over 20% of patients had a poor prognosis for knee replacement[17]. Despite this, the demand for this treatment continues to grow on a global scale, and young people account for an increasing proportion[17]. Opioid abuse and considerable growth for joint replacement requirements lead to overstretched healthcare systems. There is an urgent need to develop new treatment options, evaluate the effect of existing treatments, or optimize current approaches[18].

As an integral component of the long-standing practice of traditional Chinese medicine spanning over 4000 years, acupuncture has emerged as a safe and low-risk physical therapy with demonstrated cost-effectiveness[18-21]. Acupuncture is widely used in clinical practice to treating KOA, resulting in notable improvements in pain and joint function[18 22]. In light of these findings, the American College of Rheumatology and American Academy of Orthopaedic Surgeons have conditionally recommended the implementation of acupuncture on KOA[23 24]. The effect of acupuncture is inherently intertwined with the treatment course[19]. A cumulative course of treatment is required to produce and maintain the effect of acupuncture[19].

Currently, there is not enough evidence to make a comparison between different acupuncture courses on KOA. The 8-week acupuncture courses resulted in pain relief and improved joint function among KOA patients [25], which was consistent with our own previous research[26]. Moreover, the benefits of acupuncture on KOA persisted to 26 weeks[22 26]. A meta-analysis has shown that a minimum of 4-week acupuncture

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treatment is needed to alleviate symptoms in KOA patients[27]. Additionally, 4-week acupuncture on KOA has conferred the short-term relief of symptoms[28-32]. A secondary analysis revealed that short-term effect of acupuncture is better at week 8 than week 4 on KOA, although the growth rate of benefits slowed down with additional treatment courses[33]. More evidence is required to explain the long-term effect of acupuncture on KOA between different treatment courses. In order to adress this, We conduct a trial to evaluate the long-term effect of 4 weeks versus 8 weeks of acupuncture on KOA.

Methods

Study design

This is a pragmatic, parallel, two-arm randomized controlled research scheduled to take place at Dongzhimen Hospital and Beijing Liangxiang Hospital from August 2023 to June 2024. A total of 148 eligible patients will be assigned randomly in a 1:1 radio to receive 4-week or 8-week acupuncture. EA treatment will be administered 3 times per week for 4 or 8 weeks. KOA patients in both groups will be followed up to 26 weeks. The schedule of the assessments completed by all patients is illustrated in Table 1 and the research flow diagram is presented in Figure 1. The protocol adheres to the principles of the Declaration of Helsinki and will be reported in accordance with the SPIRIT guidelines (additional file 1).

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Table 1 the schedule of assessments

The assessments	Baseline	Week 4	Week 8	Week 16	Week 26
Response rate		×	×	×	×
NRS	×	×	×	×	×
WOMAC	×	×	×	×	×
SF-12	×	×	×	×	×
Patient global assessment	×	×	×	×	×
The OARSI response rate		×	×	×	×
Rescue medicine		×	×	×	×
Adverse events		×	×	×	×

NRS: numerical rating scale, WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index, SF-12: 12 item Short Form Health Survey, OARSI: Osteoarthritis Research Society International

Recruitment

Participants will be recruited from individuals diagnosed with KOA based on the American College of Rheumatology (ACR) criteria[34]. Announcements will be distributed through social media (WeChat), outpatient units and print advertisements. Interested patients can contact the clinical research coordinator (CRC) via telephone, e-mail, or WeChat to be enrolled in this research. The CRC will inform the study protocol in detail with them, including the purpose, procedures, time commitment, potential risks and benefits associated with participation in this trial. Following a preliminary screening process for inclusion and exclusion, potential candidates will be invited to undergo a face-to-face screening by CRC. Confidentiality measures will be taken to safeguard patient privacy. Eligible participants will sign the informed consent before randomization.

Inclusion criteria

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1. Aged 45-75 years (both genders).

2. Diagnosed with KOA according to the ACR criteria.

3. Unilateral/bilateral chronic knee pain for over 3 months.

4. Radiologic confirmation of KOA within 6 months (Kellgren–Lawrence grade II or III).

5. The average score for knee pain during walking on flat ground in the last week ≥ 4 out of 10 on a numerical rating scale (NRS)[35].

6. Written informed consent.

Exclusion criteria

1. History of knee surgery or waiting for surgery (knee replacement or arthroscopic knee surgery).

2. Knee pain caused by other diseases (autoimmune diseases, infection, malignant tumours, trauma, fracture, joint loose bodies, severe effusion of joint cavity, lumbosacral vertebrae disease, gout, etc.).

3. Arthroscopy within 1 year and intra-articular injection in the past 6 months.

4. Acupuncture treatment during the past 6 months.

5. Serious acute or chronic organ diseases or mental disorders.

6. Blood coagulation disorders.

7. Pregnancy and breastfeeding.

8. Cardiac pacemaker and epilepsy.

9. Participation in another clinical study within 1 month.

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Randomization

All eligible patients will be randomly allocated to either 4-week group or 8-week group in a 1:1 ratio through a random number sequence, which will be generated by a professional statistician who is not involved in the assessment or treatment of participants using SAS 9.3 software. A central stratified block randomized design with variable block sizes will be used in this trial. The random number sequence and treatment plans will be placed inside corresponding numbered opaque envelopes. After the baseline assessment of eligible participants by CRC, an independent research assistant who is separate from the trial will assign the envelopes to acupuncturists. The acupuncturists will ensure the envelopes are sealed and will open them to determine which intervention should be performed. The CRC will be responsible for enrolling participants, obtaining informed consent and requesting randomization.

Blinding

The outcome assessor and data analyst will be blinded to group assignments. In consideration of the nature of the intervention, the acupuncturist and patients will not be blinded. The interventions allocated to the patients will remain undisclosed until the completion of the statistical analysis.

Patient and public involvement

There is no patient or public involvement in study design, recruitment for or conduct of the study.

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Interventions

The acupuncture prescription, derived from clinical practice and a pre-study[26], comprises 5 essential acupoints and 3 adjunct acupoints. The essential acupoints consist of dubi (ST35), neixiyan (EX-LE5), ququan (LR8), xiyangguan (GB33), and an ash point (the acupoint where the patient reports the most intense pain). The acupuncturist will select appropriate adjunct acupoints based on the patient's lesion types, which has been shown in Table 2. The acupoints are localized according to the World Health Organization Standard Acupuncture Locations and are presented in Table 3 and Figure 2. Licensed acupuncturists are of minimum 5 years' experience in acupuncture. For individuals afflicted with bilateral osteoarthritis, both knees will be subjected to acupuncture needling[25]. Conversely, unilateral osteoarthritis patient only receive acupuncture therapy on the affected knee[25]. Throughout the course of the trial, patients with pain unbearable can obtain Diclofenac Sodium Enteric-coated Tables (Beijing Novartis Pharma Ag) from the CRC, who will record the use of medication. Diclofenac Sodium Enteric-coated Tables will be dispensed in sets of 6 tablets, with instructions for patients to ingest one orally three times daily.

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Table 2 The adjunct acupoints

Meridian syndrome	Acupoints
Foot yangming (anterior side of leg)	Liangqiu (ST34), zusanli (ST36), futu (ST32), fenglong (ST40), heding (EL-XE2)
Foot shaoyang (lateral side of the leg)	Fengshi (GB31), waiqiu (GB36), yanglingquan (GB34), xuanzhong (GB39), zulinqi (GB41)
Foot taiyang (posterior side of the leg)	Weiyang (BL39), weizhong (BL40), chengshan (BL57), kunlun(BL60)
Foot three-yin (medial side of the leg)	Xiguan (LR7), yinlingquan (SP9), xuehai (SP10), yingu (KI10), gongsun (SP4), sanyinjiao (SP6), taichong (LR3), taixi (KI3)

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Table 3 Acupoints manipulation

Acupoints	Angle	Depth	Twisting and reinforcing	De Qi
ST35	Oblique jab in the inner-up direction	0.5-1 inch	Even reinforcing-reducing	Yes
EX-LE5	Oblique jab in the external-superior directio	0.5-1 inch	Even reinforcing-reducing	Yes
LR8	Penetrating jab to GB33	1-1.5 inch	Reducing	Yes
GB33	Penetrating jab to LR8	1-1.5 inch	Reducing	Yes
GB34	Perpendicular inserting	1-1.5 inch	Even reinforcing-reducing	Yes
EX-LE2	Perpendicular inserting	0.8-1 inch	Even reinforcing-reducing	Yes
ST34	Perpendicular inserting	1-1.2 inch	Even reinforcing-reducing	Yes
ST36	Perpendicular inserting	1-2 inch	Reinforcing	Yes
ST40	Perpendicular inserting	1-1.5 inch	Reducing	Yes
ST32	Perpendicular inserting	1-2 inch	Reinforcing	Yes
GB31	Perpendicular inserting	1-1.5 inch	Reinforcing	Yes
GB36	Perpendicular inserting	0.5-0.8 inch	Even reinforcing-reducing	Yes
GB39	Perpendicular inserting	0.5-0.8 inch	Even reinforcing-reducing	Yes
GB41	Perpendicular inserting	0.5-0.8 inch	Even reinforcing-reducing	Yes
BL39	Perpendicular inserting	1-1.5 inch	reducing	Yes
BL40	Perpendicular inserting	1-1.5 inch	Even reinforcing-reducing	Yes
BL57	Perpendicular inserting	1.5-2 inch	Reinforcing	Yes
BL60	Perpendicular inserting	0.5-0.8 inch	Even reinforcing-reducing	Yes
KI3	Perpendicular inserting	0.5-0.8 inch	Reducing	Yes
KI10	Perpendicular inserting	1-1.5 inch	Even reinforcing-reducing	Yes
SP4	Perpendicular inserting	0.5-1.2 inch	Reducing	Yes
SP6	Perpendicular inserting	1-1.5 inch	Reinforcing	Yes
LR3	Perpendicular inserting	0.5-0.8 inch	Even reinforcing-reducing	Yes
LR7	Perpendicular inserting	1-1.5 inch	Even reinforcing-reducing	Yes
SP9	Perpendicular inserting	1.5-2 inch	Reducing	Yes
SP10	Perpendicular inserting	1-2 inch	Even reinforcing-reducing	Yes

Reinforcing: angle ＜90°, frequency ＞120r/min; Even reinforcing-reducing: angle between 120° and 180°, frequency between 60 and 120r/min; reducing: angle＞180°, frequency ＜ 60r/min

4-week group

Acupuncture treatments will consist of 12 sessions, each lasting 30 minutes, and will be administered 3 times per week over 4 weeks. Single-use aseptic needles (length: 25-40mm, diameter: 0.25mm, Hwato, Suzhou, China) will be used. Before needle

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insertion, both acupuncturist's hands and acupuncture site will be strictly disinfected with 75% alcohol. Then acupuncturists will proceed to apply the needles through the skin, selecting the appropriate acupuncture angle, depth, and manipulation technique as per Table 3. In order to achieve the sensation of "De Qi" (a composite sensation characterized by soreness, numbness, distention or heaviness), needles will be manually stimulated for a duration of 10s. Paired electrodes from an EA apparatus (HANS-200A acupoint nerve stimulator; Jisheng, Nanjing, China) will be attached to needle holders at LR 8-GB 33 and 2 adjunct acupoints. The electro-acupuncture stimulation will be a dilatation wave of 2/100 Hz, depending on the patient's comfort level.

8-week group

Acupuncture treatments will consist of 24 sessions, each lasting 30 minutes, and will be administered 3 times per week over 8 weeks. All other procedures will remain consistent with 4-week group. The differences and similarities between two groups are shown in Supplemental Table 1.

Outcomes

If patients with unilateral osteoarthritis, the evaluation of outcomes will pertain exclusively to that knee. For bilateral osteoarthritis, the knee with worse symptoms at baseline will be assessed.

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Primary outcome

The primary outcome is the response rate at week 26, which is defined as the proportion of patients achieving a minimal clinically important improvement (MCII)[36]. Specifically, the MCII is a ≥ 2-point improvement on the NRS and a ≥ 6-point improvement on the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) function score compared to baseline[36]. An 11-point NRS ranges from 'absence of pain' (0) to 'most intense pain imaginable' (10). The WOMAC function subscale scored from 0 to 68 will be used to evaluate the mean knee discomfort experienced over the preceding week, with lower scores indicating better functional ability.

Secondary outcomes

Response rate at other time points The response rate will be assessed at weeks 4, 8 and 16.

Knee-joint pain The mean pain experienced within the preceding week will be measured using an 11-point NRS and the WOMAC pain subscale at weeks 0, 4, 8, 16 and 26. The WOMAC pain subscale spanning from 0 to 20 comprises 5 items[37]. Higher scores are indicative of increased pain.

Knee-joint function The average function of the last 7 days will be measured using the WOMAC function subscale at weeks 0, 4, 8, 16 and 26. The tool spans across a range

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of 0 to 68, encompassing 17 items. Lower scores on this subscale are indicative of superior physical function[37].

Knee-joint stiffness The mean stiffness throughout the preceding week will be assessed via the WOMAC stiffness subscale at weeks 0, 4, 8, 16 and 26. The WOMAC stiffness subscale ranges from 0 to 8, including 2 items, with higher scores indicating increased stiffness[37].

Quality of life The evaluation for the standard of living will be performed at weeks 0, 4, 8, 16 and 26, following the randomization process, by mean of the 12 item Short Form Health Survey (SF-12)[38]. The SF-12 comprises of both mental and physical domains, and each domain is calibrated from 0 to 100. Higher scores on the scale indicate an improved quality of life.

Patient global assessment The singular item of the patient global assessment concerns the knee symptoms experienced by participants during the preceding week. Utilizing the Visual Analogue Scale, which ranges from 0 to 100, the severity of the disease is positively correlated with the magnitude of the score. This inquiry will be administered at weeks 0, 4, 8, 16 and 26.

The Osteoarthritis Research Society International (OARSI) response rate The proportion of subjects with improvement in pain or function ≥ 50% and absolute

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change ≥20, or enhancement in a minimum of 2 of the following: pain ≥20% and absolute change ≥10, function ≥20% and absolute change ≥10, and patient's global assessment ≥20% and absolute change ≥10[39]. The OARSI response rate will be assessed at weeks 4, 8, 16 and 26.

Rescue medicine Any use of Diclofenac Sodium Enteric-coated Tables will be quantified at weeks 4, 8, 16 and 26.

Safety

For adverse events that occur during the trial, researchers should record the appearance time, duration, classification, severity, remedial actions taken, remedial process, final resolution, etc. on the case report form (CRF). Moreover, researchers will assess the correlation between the intervention and the adverse event, in conjunction with other potential causative and confounding factors, in a comprehensive manner. In the event of serious adverse occurrences, researchers should immediately address and report to the principal investigator. Adverse events comprise subcutaneous hematoma, unrelenting post-injection pain, pruritus at the needle puncture location, etc. It is imperative that all adverse events are meticulously tracked until resolution or stabilization is achieved.

Simple size

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Drawing upon the team's prior research, the anticipated response rates for the 4-week and 8-week groups are 35% and 60%[26]. The sample size of 59 patients in each group was calculated to provide 80% power, with a two-tailed α level of 0.05, utilizing PASS15.05 software. This requires 74 patients per group allowing for 20% dropout.

Statistical analysis

Using IBM SPSS 26.0 software for statistical analysis, $P < 0.05$ will be deemed statistically significant. Mean ± standard deviation will be utilized to measurement data, while percentages will be used to enumeration data. All randomized cases will be included into intention-to-treat analysis, and missing data will be filled in using multiple imputation. Per protocol analysis will only include the cases that fully complied with the trial protocol and will be used for the primary outcome as sensitivity analysis. Measurement data conforming to normal distribution will undergo *t*-test analysis, while measurement data not normal distribution will be subjected to Mann-Whitney test. Enumeration data will be analyzed via χ^2 test or Fisher 's exact test. 4-week and 8-week groups will be assessed the cost effectiveness of acupuncture over 26 weeks.

Data management

Data collector and entry clerks, data manager, statistician and outcome assessor will undergo training in data management. At the end of the treatment phase, all participant data will be completed and recorded on the original CRFs. The data will be entered

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into Excel spreadsheets by the data entry clerks in time, following which the accuracy of the 2 datasets will be compared by the data manager. Any discrepancies will be corrected in accordance with the original CRFs.

All paper files related to the research will be preserved, and electronic documents will be securely stored on a password-protected computer. These research documents, whether in paper or electronic form, will be retained for a minimum of 5 years following publication. If readers and reviewers have any questions regarding our published data, they can contact the corresponding author to request the original data. Patient private information, including their name and telephone number, will be safeguarded.

Quality control

Patients will be included in strict accordance with diagnosis, inclusion and exclusion criteria. Standard operating procedures was developed for each aspect of the trial to ensure uniformity in its implementation and provide a reference in case of disagreements. Researchers will undergo uniform training that cover the study objectives, treatment standards, random allocation, acupuncture techniques, and assessment forms. And they should strictly follow the subject design plan, fill in the CRF carefully and objectively, and record truthfully all kinds of problems that arise in the clinical trial. Compliance control will be reinforced by registering participants' contact information and then making an appointment in advance for them to come to

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the treatment. The inspector will regularly check the trial records. Any problems encountered will be reported to the supervisor promptly, and strict measures will be taken to identify and solve them.

Discussion

KOA represents a prevalent and incapacitating desease, constituting a considerable public health concern. Currently, there is a paucity of evidence comparing diverse acupuncture courses, with regards to their effect in treating KOA. The research aims to evaluate the long-term effect of 4 weeks versus 8 weeks of acupuncture on KOA.

Our clinical trial incorporates rigorous scientific methodologies and comprehensive outcome measures to assess treatment response, and we will provide a high-quality report on the difference in acupuncture treatment effect between 4 and 8 weeks. It is an innovative and practical approach, and the research will provide strong clinical evidence of effect of various acupuncture treatment courses. All participants will receive acupuncture treatment throughout the trial, without a placebo control group, which will promote their compliance. During the trial, various researchers will be responsible for the generation, concealment and allocation of the random number sequence, patients' recruitment, acupuncture treatment and outcome measure assessment. Such a division of labor will ensure that randomization is fully maintained, thus controlling for selection bias and confounding bias to ensure comparability between two groups.

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There are, however, 3 limitations to this trial. Firstly, the nature of the intervention precludes the possibility of blinding both acupuncturists and patients. But data analysts and outcome assessors will be blinded, and acupuncturists will receive training on how to minimize bias by interacting less with patients. Sceondly, only patients with KL II or III will be included in this trial and results of the research will not be generalized to patients with KL IV, who might require longer treatment courses. Thirdly, the trial only compared two common treatment courses of acupuncture, 4 weeks and 8 weeks, without any comparison to other courses.

In conclusion, these findings will enhance the high-quality evidence on the effect of different acupuncture treatment courses. Furthermore, this research will provide invaluable insights for developing effective and practical treatment plans for KOA patients. It will help make medical decisions, improve health insurance reimbursement programs, and ensure efficient allocation of precious healthcare resources.

Trial status

This trial is currently recruiting participants.

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Authors' contributions

J-FT conceived the research. J-FT and YY initiated the research design. YY, J-FT, and C-ZL drafted and critically revised the manuscript for important intellectual content. C-ZL sought funding and ethical approval. All authors contributed to the refinement of the research protocol and approved the final manuscript.

Ethics declarations

The study has obtained ethics approval from the Research Ethical Committee of Beijing University of Chinese Medicine (No.2023BZYL0506). It has been registered on Chinese Clinical Trials Registry (No.ChiCTR2300073383). The participants will be made aware that their information and data will be kept anonymous and confidential. They can make the decision to withdraw from the trial at any time. All information will be encrypted and only the designated researcher will access to it.

Competing interests

The authors declare that they have no competing interests.

References

1. Katz JN, Arant KR, Loeser RF. Diagnosis and Treatment of Hip and Knee Osteoarthritis: A Review. *JAMA* 2021;325(6):568-78. doi: 10.1001/jama.2020.22171

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

2. Hunter DJ, Bierma-Zeinstra S. Osteoarthritis. *Lancet* 2019;393(10182):1745-59. doi: 10.1016/S0140-6736(19)30417-9

3. Safiri S, Kolahi AA, Smith E, et al. Global, regional and national burden of osteoarthritis 1990-2017: a systematic analysis of the Global Burden of Disease Study 2017. *Ann Rheum Dis* 2020;79(6):819-28. doi: 10.1136/annrheumdis-2019-216515

4. Chen AT, Shrestha S, Collins JE, et al. Estimating contextual effect in nonpharmacological therapies for pain in knee osteoarthritis: a systematic analytic review. *Osteoarthritis Cartilage* 2020;28(9):1154-69. doi: 10.1016/j.joca.2020.05.007

5. Silverwood V, Blagojevic-Bucknall M, Jinks C, et al. Current evidence on risk factors for knee osteoarthritis in older adults: a systematic review and meta-analysis. *Osteoarthritis Cartilage* 2015;23(4):507-15. doi: 10.1016/j.joca.2014.11.019

6. Cross M, Smith E, Hoy D, et al. The global burden of hip and knee osteoarthritis: estimates from the global burden of disease 2010 study. *Ann Rheum Dis* 2014;73(7):1323-30. doi: 10.1136/annrheumdis-2013-204763

7. Hardenberg M, Spekle EM, Coenen P, et al. The economic burden of knee and hip osteoarthritis: absenteeism and costs in the Dutch workforce. *BMC Musculoskelet Disord* 2022;23(1):364. doi: 10.1186/s12891-022-05306-9

8. Nelson AE, Allen KD, Golightly YM, et al. A systematic review of recommendations and guidelines for the management of osteoarthritis: The chronic osteoarthritis management initiative of the U.S. bone and joint initiative. *Semin Arthritis Rheum* 2014;43(6):701-12. doi: 10.1016/j.semarthrit.2013.11.012

9. da Costa BR, Reichenbach S, Keller N, et al. Effectiveness of non-steroidal anti-

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inflammatory drugs for the treatment of pain in knee and hip osteoarthritis: a network meta-analysis. *Lancet* 2017;390(10090):e21-e33. doi: 10.1016/S0140-6736(17)31744-0

10. da Costa BR, Reichenbach S, Keller N, et al. RETRACTED: Effectiveness of non-steroidal anti-inflammatory drugs for the treatment of pain in knee and hip osteoarthritis: a network meta-analysis. *Lancet* 2016;387(10033):2093-105. doi: 10.1016/S0140-6736(16)30002-2
11. Juni P, Hari R, Rutjes AW, et al. Intra-articular corticosteroid for knee osteoarthritis. *Cochrane Database Syst Rev* 2015;2015(10):CD005328. doi: 10.1002/14651858.CD005328.pub3
12. Orchard JW. Is there a place for intra-articular corticosteroid injections in the treatment of knee osteoarthritis? *BMJ* 2020;368:l6923. doi: 10.1136/bmj.l6923
13. Cepeda MS, Camargo F, Zea C, et al. Tramadol for osteoarthritis: a systematic review and metaanalysis. *J Rheumatol* 2007;34(3):543-55
14. da Costa BR, Nuesch E, Kasteler R, et al. Oral or transdermal opioids for osteoarthritis of the knee or hip. *Cochrane Database Syst Rev* 2014(9):CD003115. doi: 10.1002/14651858.CD003115.pub4
15. da Costa BR, Pereira TV, Saadat P, et al. Effectiveness and safety of non-steroidal anti-inflammatory drugs and opioid treatment for knee and hip osteoarthritis: network meta-analysis. *BMJ* 2021;375:n2321. doi: 10.1136/bmj.n2321
16. Osani MC, Lohmander LS, Bannuru RR. Is There Any Role for Opioids in the Management of Knee and Hip Osteoarthritis? A Systematic Review and Meta-Analysis. *Arthritis Care Res (Hoboken)* 2021;73(10):1413-24. doi: 10.1002/acr.24363 [published Online First: 2020/06/26]

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17. Price AJ, Alvand A, Troelsen A, et al. Knee replacement. *Lancet* 2018;392(10158):1672-82. doi: 10.1016/S0140-6736(18)32344-4

18. Hunter DJ, Harris RE. Acupuncture and Knee Osteoarthritis: Does Dose Matter? *Arthritis Rheumatol* 2021;73(3):371-73. doi: 10.1002/art.41583 [published Online First: 2020/11/11]

19. Chon TY, Lee MC. Acupuncture. *Mayo Clin Proc* 2013;88(10):1141-6. doi: 10.1016/j.mayocp.2013.06.009

20. Witt CM, Reinhold T, Jena S, et al. Cost-effectiveness of acupuncture treatment in patients with headache. *Cephalalgia* 2008;28(4):334-45. doi: 10.1111/j.1468-2982.2007.01504.x

21. MacPherson H, Thomas K, Walters S, et al. The York acupuncture safety study: prospective survey of 34 000 treatments by traditional acupuncturists. *BMJ* 2001;323(7311):486-7. doi: 10.1136/bmj.323.7311.486

22. Vickers AJ, Vertosick EA, Lewith G, et al. Acupuncture for Chronic Pain: Update of an Individual Patient Data Meta-Analysis. *J Pain* 2018;19(5):455-74. doi: 10.1016/j.jpain.2017.11.005

23. Kolasinski SL, Neogi T, Hochberg MC, et al. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Management of Osteoarthritis of the Hand, Hip, and Knee. *Arthritis Rheumatol* 2020;72(2):220-33. doi: 10.1002/art.41142

24. Brophy RH, Fillingham YA. AAOS Clinical Practice Guideline Summary: Management of Osteoarthritis of the Knee (Nonarthroplasty), Third Edition. *J Am Acad Orthop Surg* 2022;30(9):e721-e29. doi: 10.5435/JAAOS-D-21-01233

25. Witt C, Brinkhaus B, Jena S, et al. Acupuncture in patients with osteoarthritis of the knee: a randomised trial. *Lancet* 2005;366(9480):136-43. doi: 10.1016/S0140-6736(05)66871-7

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

26. Tu JF, Yang JW, Shi GX, et al. Efficacy of Intensive Acupuncture Versus Sham Acupuncture in Knee Osteoarthritis: A Randomized Controlled Trial. *Arthritis Rheumatol* 2021;73(3):448-58. doi: 10.1002/art.41584

27. Chen N, Wang J, Mucelli A, et al. Electro-Acupuncture is Beneficial for Knee Osteoarthritis: The Evidence from Meta-Analysis of Randomized Controlled Trials. *Am J Chin Med* 2017;45(5):965-85. doi: 10.1142/S0192415X17500513

28. Chen Y, Jia YJ, Lu JH, et al. [Comparision of therapertic effect of different acupuncture methods for knee osteoarthritis]. *Zhen Ci Yan Jiu* 2020;45(7):569-73. doi: 10.13702/j.1000-0607.191015

29. Bao F, Zhang Y, Wu ZH, et al. [Efficacy observation on knee osteoarthritis treated with electroacupuncture and its influence on articular cartilage with T2 mapping]. *Zhongguo Zhen Jiu* 2013;33(3):193-7

30. Sangdee C, Teekachunhatean S, Sananpanich K, et al. Electroacupuncture versus diclofenac in symptomatic treatment of osteoarthritis of the knee: a randomized controlled trial. *BMC Complement Altern Med* 2002;2:3. doi: 10.1186/1472-6882-2-3

31. Huang DE, Qin Y, Lin MN, et al. [Clinical efficacy of different waves of electroacupuncture on knee osteoarthritis and its effect on TGF-beta1 in joint fluid]. *Zhongguo Zhen Jiu* 2020;40(4):370-4. doi: 10.13703/j.0255-2930.20190422-0005

32. Lu N, Cheng P, Xia JX, et al. [Effect of acupuncture combined with moxibustion on serum matrix metalloproteinase-9 and matrix metalloproteinase inhibitor-1 in patients with knee osteoarthritis]. *Zhen Ci Yan Jiu* 2022;47(3):262-7. doi: 10.10372/j.1000-0607.20210079

33. Yu Y KS, Tu JF, et al Influence of intervention period on the effect of acupuncture in knee

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

osteoarthritis: a secondary analysis of a multi-center randomized controlled trial. *World J Acupunct Moxibustion* 2023 in press

34. Hochberg MC, Altman RD, Brandt KD, et al. Guidelines for the medical management of osteoarthritis. Part II. Osteoarthritis of the knee. American College of Rheumatology. *Arthritis Rheum* 1995;38(11):1541-6. doi: 10.1002/art.1780381104
35. Jensen MP, Karoly P, Braver S. The measurement of clinical pain intensity: a comparison of six methods. *Pain* 1986;27(1):117-26. doi: 10.1016/0304-3959(86)90228-9
36. Tubach F, Ravaud P, Baron G, et al. Evaluation of clinically relevant changes in patient reported outcomes in knee and hip osteoarthritis: the minimal clinically important improvement. *Ann Rheum Dis* 2005;64(1):29-33. doi: 10.1136/ard.2004.022905
37. Bellamy N, Buchanan WW, Goldsmith CH, et al. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. *J Rheumatol* 1988;15(12):1833-40
38. Ware J, Jr., Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. *Med Care* 1996;34(3):220-33. doi: 10.1097/00005650-199603000-00003
39. Pham T, Van Der Heijde D, Lassere M, et al. Outcome variables for osteoarthritis clinical trials: The OMERACT-OARSI set of responder criteria. *J Rheumatol* 2003;30(7):1648-54

Figure legends

Figure 1 The flow diagram of the trial

KOA: knee osteoarthritis

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Figure 2 Meridian acupoints chart

Red points: obligatory acupoints; blue points: foot yangming meridian syndrome; purple points: foot shaoyang meridian syndrome; yellow points: foot taiyang meridian syndrome; green points: foot three-yin meridian syndrome

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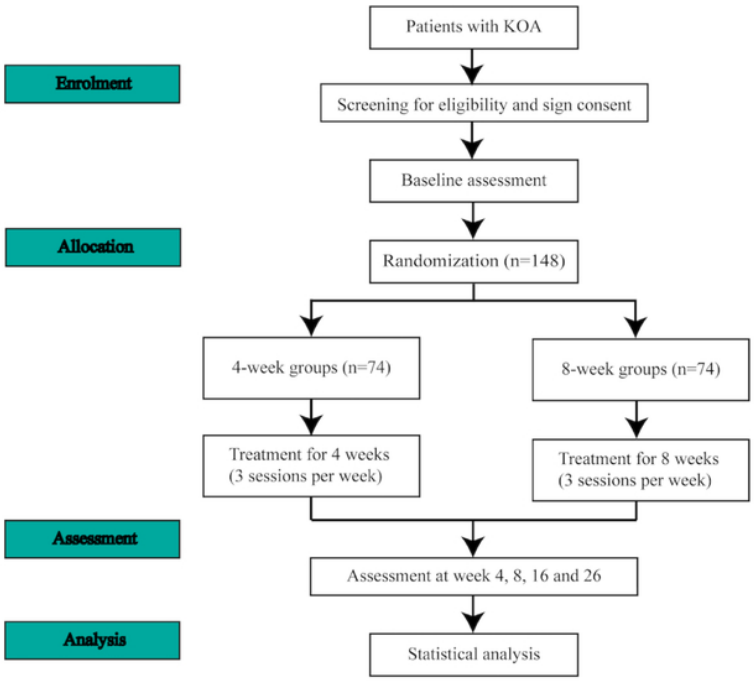
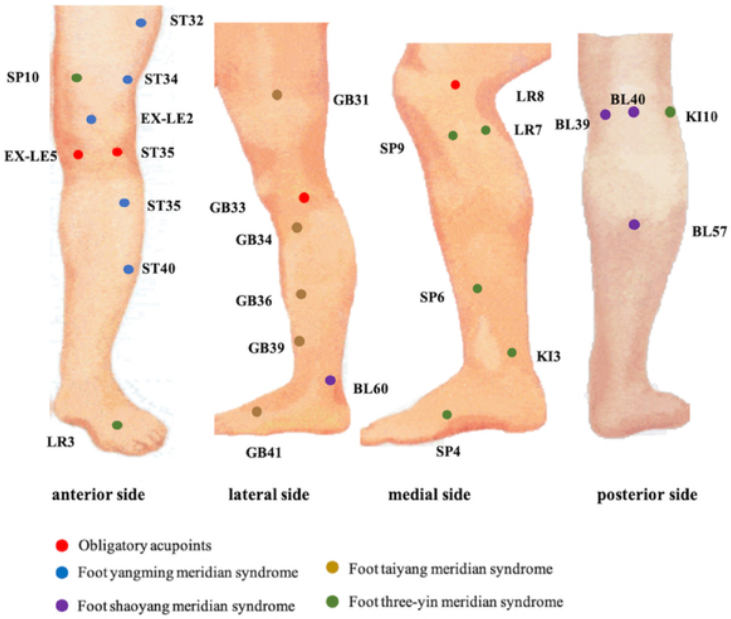


KOA: knee osteoarthritis

34x25mm (600 x 600 DPI)



Red points: obligatory acupoints; blue points: foot yangming meridian syndrome; purple points: foot shaoyang meridian syndrome; yellow points: foot taiyang meridian syndrome; green points: foot three-yin meridian syndrome

33x20mm (600 x 600 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Page
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	5-16
Protocol version	3	Date and version identifier	3
Funding	4	Sources and types of financial, material, and other support	20
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1-2,21
	5b	Name and contact information for the trial sponsor	20
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	20
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	15-16

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*(continued)

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Section/item	Item No	Description	Page
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5-6
	6b	Explanation for choice of comparators	5-6,18
Objectives	7	Specific objectives or hypotheses	6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6-7
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7-8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9-12
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	Not applicable

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*(continued)

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Section/item	Item No	Description	Page
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	9
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	9
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	12-15
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	6-7, Figure 1, Table 4
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	16-17
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	7
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	8-9

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*(continued)

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Section/item	Item No	Description	Page
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	8-9
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8-9
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	9
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	9
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	15-16
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	15-16
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	15-16
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	17-18

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*(continued)

Section/item	Item No	Description	Page
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	17-18
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	17-18
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	16
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	Not applicable
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	15
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	15-16
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	21
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	Not applicable

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*(continued)

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Section/item	Item No	Description	Page
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Not applicable
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	15
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	21-22
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	20-21
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	Not applicable
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	20-21
	31b	Authorship eligibility guidelines and any intended use of professional writers	20-21
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Not applicable

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*(continued)

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Section/item	Item No	Description	Page
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	supplementary file
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Not applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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Supplemental Table 1 Differences and similarities for 4-week group and 8-week group

	4-week group	8-week group
Course	4 weeks	8 weeks
Session	12 sessions	24 sessions
Frequency	3 times per week	3 times per week
Duration	30 minutes each	30 minutes each
Acupoint	5 essential acupoints and 3 adjunct acupoints	5 essential acupoints and 3 adjunct acupoints
EA stimulation	a dilatation wave of 2/100 Hz	a dilatation wave of 2/100 Hz

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BMJ Open

Effect of 4 weeks versus 8 weeks of acupuncture for knee osteoarthritis in China: protocol for a randomized controlled trial

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Keywords:	COMPLEMENTARY MEDICINE, Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Musculoskeletal disorders < ORTHOPAEDIC & TRAUMA SURGERY

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Manuscripts

Effect of 4 weeks versus 8 weeks of acupuncture for knee osteoarthritis in China: protocol for a randomized controlled trial

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Abstract

Introduction Knee osteoarthritis represents the prevalent and incapacitating disease. Acupuncture, a widely used clinical treatment for knee osteoarthritis, has been shown to ameliorate pain and enhance joint function in affected individuals. However, there is a lack of evidence comparing different courses of acupuncture for knee osteoarthritis. In this trial, we will assess the effect of 4 weeks versus 8 weeks of acupuncture in patients with knee osteoarthritis.

Methods and analysis The protocol is a pragmatic, parallel, two-armed randomized controlled trial, with data analyst and assessor being blinded. 148 eligible patients with knee osteoarthritis will be randomly allocated in a 1:1 radio to receive 4-week or 8-week acupuncture. Electro-acupuncture will be administered 3 times per week for 4 or 8 weeks, respectively. Patients with knee osteoarthritis in both groups will be followed up to 26 weeks. The primary outcome is the response rate at week 26, and secondary outcomes include knee-joint pain, knee-joint function, knee-joint stiffness, quality of life, patient global assessment, the Osteoarthritis Research Society International response rate and rescue medicine. A cost-effectiveness analysis will be carried out over 26 weeks.

Ethics and dissemination The protocol has been approved by the Medical Ethical Committee of Beijing University of Chinese Medicine (2023BZYL0506). The study findings will be disseminated through presentation in a medical journal. Additionally, we plan to present them at select conferences and scientific meetings.

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Trial registration The trial has been registered in the Chinese Clinical Trials Registry (ChiCTR2300073383. Register date: July 10, 2023, *https://www.chictr.org.cn/showproj.html?proj=199310*).

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Strengths and limitations of this study

1. Different courses of acupuncture for KOA will be head-to-head compared in this randomized controlled trial.
2. During the trial, various researchers will be responsible for the generation of the random number sequence, allocation concealment, patients' recruitment, acupuncture treatment and outcome measure assessment to control bias.
3. Cost effectiveness of acupuncture will be assessed over 26 weeks in both 4-week and 8-week groups.
4. The nature of the intervention precludes the possibility of blinding both acupuncturists and patients, which may bring bias.
5. The trial only compared 2 common treatment courses of acupuncture, 4 weeks and 8 weeks, without any comparison to other courses.

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Background

Osteoarthritis, a degenerative joint disease, is a prevalent affliction among adults globally, with the knee joint being the most commonly affected[1 2]. Estimates published in 2020 suggest that 300 million people worldwide are affected by hip and knee osteoarthritis (KOA)[3]. KOA is characterized by pain and functional limitations, which impairs patients' quality of life seriously[2 4], with age, gender, obesity, excessive physical activities and previous knee trauma being some of the associated risk factors[1 5]. Of note, female patients are more likely to suffer from KOA compared to males[1 6]. And the incidence of KOA increases with age, making it a major contributor to disability in elderly population[1 6]. The annual sick leave costs due to knee and hip osteoarthritis are about €40 million for the Dutch workforce, and KOA costs approximately twice as much as hip osteoarthritis[7]. KOA reduces the employability of patients and raises the cost of healthcare, which places a heavy financial burden on individuals and society.

Exercise therapy and weight loss have been shown to be effective in KOA[1], but sustained maintenance of these methods persists as a challenge[2] due to depending heavily on patient compliance[1]. Acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs) are strongly recommended for KOA patients in the guideline[8]. Nonetheless, using acetaminophen alone is not much of a role[9]. Taking into consideration the potential gastrointestinal and cardiovascular side effect, NSAIDs should be used for shortest duration possible[10]. Intra-articular corticosteroid injections

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may be an effective management strategy for KOA patients, but prolonged usage increases the risk of joint deterioration[11 12]. Opioid has limited benefits for KOA and a elevated risk of the gastrointestinal adverse event or somnolence[13-16]. Over 20% of patients had a poor prognosis for knee replacement[17]. Despite this, the demand for this treatment continues to grow on a global scale, and young people account for an increasing proportion[17]. Opioid abuse and considerable growth for joint replacement requirements lead to overstretched healthcare systems. Urgent research is required to to develop new treatment options, evaluate the effect of existing treatments, or enhance current approaches[21].

As an integral component of the long-standing practice of traditional Chinese medicine spanning over 4000 years, acupuncture has emerged as a safe and low-risk physical therapy with demonstrated cost-effectiveness[21-24]. Acupuncture is widely used in clinical practice to treating KOA, resulting in notable improvements in pain and joint function[21 25 26]. In light of these findings, the American College of Rheumatology and American Academy of Orthopaedic Surgeons have conditionally recommended the implementation of acupuncture on KOA[20 27]. The effect of acupuncture is inherently intertwined with the treatment course[22 28]. A cumulative course of treatment is required to produce and maintain the effect of acupuncture[22].

Currently, there is a paucity of evidence about head-to-head comparison of diverse acupuncture courses, with regards to their effect in treating KOA. The 8-week

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acupuncture courses resulted in pain relief and improved joint function among KOA patients [29], which was consistent with our own previous research[30]. A meta-analysis has shown that a minimum of 4-week acupuncture treatment is needed to alleviate symptoms in KOA patients[31]. Additionally, other studies also have shown that 4-week acupuncture for KOA can conferred the relief patients' pain and dysfunction[32-36]. 4–8 weeks of acupuncture for KOA is recommended by the latest clinical practice guideline[37]. However, it is unclear which course of acupuncture is more effective, 8 weeks or 4 weeks for KOA[38]. More evidence is required to explain the effect of acupuncture on KOA between different treatment courses. In order to address this, we conduct a trial to evaluate the effect of 4 weeks versus 8 weeks of acupuncture on KOA.

Methods

Study design

This is a pragmatic, parallel, two-arm randomized controlled research scheduled to take place at Dongzhimen Hospital and Beijing Liangxiang Hospital from August 2023 to June 2024. A total of 148 eligible patients will be assigned randomly in a 1:1 radio to receive 4-week or 8-week acupuncture. Electro-acupuncture (EA) treatment will be administered 3 times per week for 4 or 8 weeks. KOA patients in both groups will be followed up to 26 weeks. The schedule of the assessments completed by all patients is illustrated in Figure 1 and the research flow diagram is presented in Figure 2. The

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protocol adheres to the principles of the Declaration of Helsinki and will be reported in accordance with the SPIRIT guidelines (additional file 1)[39].

Recruitment

Participants will be recruited from individuals diagnosed with KOA based on the American College of Rheumatology (ACR) criteria[40]. Announcements will be distributed through social media (WeChat), outpatient units and print advertisements. Interested patients can contact the clinical research coordinator (CRC) via telephone, e-mail, or WeChat to be enrolled in this research. The CRC will inform the study protocol in detail with them, including the purpose, procedures, time commitment, potential risks and benefits associated with participation in this trial. Following a preliminary screening process for inclusion and exclusion, potential candidates will be invited to undergo a face-to-face screening by CRC, who will advise patients to maintain their existing lifestyle. Confidentiality measures will be taken to safeguard patient privacy. Eligible participants will sign the informed consent before randomization.

Inclusion criteria

1. Aged 45-75 years (both genders).

2. Diagnosed with KOA according to the ACR criteria.

3. Unilateral/bilateral chronic knee pain for over 3 months.

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4. Radiologic confirmation of KOA within 6 months (Kellgren–Lawrence grade II or III).

5. The average score for knee pain during walking on flat ground in the last week ≥ 4 out of 10 on a numerical rating scale (NRS)[41].

6. Written informed consent.

Exclusion criteria

1. History of knee surgery or waiting for surgery (knee replacement or arthroscopic knee surgery).

2. Knee pain caused by other diseases (autoimmune diseases, infection, malignant tumours, trauma, fracture, joint loose bodies, severe effusion of joint cavity, lumbosacral vertebrae disease, gout, etc.).

3. Arthroscopy within 1 year and intra-articular injection in the past 6 months.

4. Acupuncture treatment during the past 6 months.

5. Serious acute or chronic organ diseases or mental disorders.

6. Blood coagulation disorders.

7. Pregnancy and breastfeeding.

8. Cardiac pacemaker and epilepsy.

9. Participation in another clinical study within 1 month.

Randomization

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All eligible patients will be randomly allocated to either 4-week group or 8-week group in a 1:1 ratio through a random number sequence, which will be generated by a professional statistician who is not involved in the assessment or treatment of participants using SAS 9.3 software. This trial will use stratified block randomisation, stratified by centre, with variable block length. The random number sequence and treatment plans will be placed inside corresponding numbered opaque envelopes. After the baseline assessment of eligible participants by CRC, an independent research assistant who is separate from the trial will assign the envelopes to acupuncturists. The acupuncturists will ensure the envelopes are sealed and will open them to determine which intervention should be performed. The CRC will be responsible for enrolling participants, obtaining informed consent and requesting randomization.

Blinding

In consideration of the nature of the intervention, the acupuncturist and patients will not be blinded. The outcome assessor and data analyst will be blinded to group assignments. The allocation will remain undisclosed to outcome assessor and data analyst until the completion of the statistical analysis.

Patient and public involvement

There is no patient or public involvement in study design, recruitment for or conduct of the study.

Interventions

The acupuncture prescription, derived from clinical practice and a pre-study[30], comprises 5 essential acupoints and 3 adjunct acupoints. The essential acupoints

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consist of dubi (ST35), neixiyan (EX-LE5), ququan (LR8), xiyangguan (GB33), and an ash point (the acupoint where the patient reports the most intense pain). The acupuncturist will select appropriate adjunct acupoints based on the patient's lesion types, which has been shown in Table 1. The acupoints are localized according to the World Health Organization Standard Acupuncture Locations and are presented in Table 2 and Figure 3. Licensed acupuncturists are of minimum 5 years' experience in acupuncture. For individuals afflicted with bilateral osteoarthritis, both knees will be subjected to acupuncture needling[29]. Conversely, unilateral osteoarthritis patient only receive acupuncture therapy on the affected knee[29]. Throughout the course of the trial, patients with pain unbearable can obtain Diclofenac Sodium Enteric-coated Tables (Beijing Novartis Pharma Ag) from the CRC, who will record the use of medication. Diclofenac Sodium Enteric-coated Tables will be dispensed in sets of 6 tablets, 25 mg per tablet, with instructions for patients to ingest one orally three times daily.

Table 1 The adjunct acupoints

Meridian syndrome	Acupoints
Foot yangming (anterior side of leg)	Liangqiu (ST34), zusanli (ST36), futu (ST32), fenglong (ST40), heding (EL-XE2)
Foot shaoyang (lateral side of the leg)	Fengshi (GB31), waiqiu (GB36), yanglingquan (GB34), xuanzhong (GB39), zulinqi (GB41)
Foot taiyang (posterior side of the leg)	Weiyang (BL39), weizhong (BL40), chengshan (BL57), kunlun(BL60)
Foot three-yin (medial side of the leg)	Xiguan (LR7), yinlingquan (SP9), xuehai (SP10), yingu (KI10), gongsun (SP4), sanyinjiao (SP6), taichong (LR3), taixi (KI3)

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Table 2 Acupoints manipulation

Acupoints	Angle	Depth	Twisting and reinforcing	De Qi
ST35	Oblique jab in the inner-up direction	0.5-1 inch	Even reinforcing-reducing	Yes
EX-LE5	Oblique jab in the external-superior directio	0.5-1 inch	Even reinforcing-reducing	Yes
LR8	Penetrating jab to GB33	1-1.5 inch	Reducing	Yes
GB33	Penetrating jab to LR8	1-1.5 inch	Reducing	Yes
GB34	Perpendicular inserting	1-1.5 inch	Even reinforcing-reducing	Yes
EX-LE2	Perpendicular inserting	0.8-1 inch	Even reinforcing-reducing	Yes
ST34	Perpendicular inserting	1-1.2 inch	Even reinforcing-reducing	Yes
ST36	Perpendicular inserting	1-2 inch	Reinforcing	Yes
ST40	Perpendicular inserting	1-1.5 inch	Reducing	Yes
ST32	Perpendicular inserting	1-2 inch	Reinforcing	Yes
GB31	Perpendicular inserting	1-1.5 inch	Reinforcing	Yes
GB36	Perpendicular inserting	0.5-0.8 inch	Even reinforcing-reducing	Yes
GB39	Perpendicular inserting	0.5-0.8 inch	Even reinforcing-reducing	Yes
GB41	Perpendicular inserting	0.5-0.8 inch	Even reinforcing-reducing	Yes
BL39	Perpendicular inserting	1-1.5 inch	reducing	Yes
BL40	Perpendicular inserting	1-1.5 inch	Even reinforcing-reducing	Yes
BL57	Perpendicular inserting	1.5-2 inch	Reinforcing	Yes
BL60	Perpendicular inserting	0.5-0.8 inch	Even reinforcing-reducing	Yes
KI3	Perpendicular inserting	0.5-0.8 inch	Reducing	Yes
KI10	Perpendicular inserting	1-1.5 inch	Even reinforcing-reducing	Yes
SP4	Perpendicular inserting	0.5-1.2 inch	Reducing	Yes
SP6	Perpendicular inserting	1-1.5 inch	Reinforcing	Yes
LR3	Perpendicular inserting	0.5-0.8 inch	Even reinforcing-reducing	Yes
LR7	Perpendicular inserting	1-1.5 inch	Even reinforcing-reducing	Yes
SP9	Perpendicular inserting	1.5-2 inch	Reducing	Yes
SP10	Perpendicular inserting	1-2 inch	Even reinforcing-reducing	Yes

Reinforcing: angle ＜90°, frequency ＞120r/min; Even reinforcing-reducing: angle between 120° and 180°, frequency between 60 and 120r/min; reducing: angle＞180°, frequency ＜ 60r/min

4-week group

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Acupuncture treatments will consist of 12 sessions, each lasting 30 minutes, and will be administered 3 times per week over 4 weeks. Single-use aseptic needles (length: 25-40mm, diameter: 0.25mm, Hwato, Suzhou, China) will be used. Before needle insertion, both acupuncturist's hands and acupuncture site will be strictly disinfected with 75% alcohol. Then acupuncturists will proceed to apply the needles through the skin, selecting the appropriate acupuncture angle, depth, and manipulation technique as per Table 2. In order to achieve the sensation of "De Qi" (a composite sensation characterized by soreness, numbness, distention or heaviness), needles will be manually stimulated for a duration of 10s. Paired electrodes from an EA apparatus (HANS-200A acupoint nerve stimulator; Jisheng, Nanjing, China) will be attached to needle holders at LR 8-GB 33 and 2 adjunct acupoints. The electro-acupuncture stimulation will be a dilatation wave of 2/100 Hz, depending on the patient's comfort level.

8-week group

Acupuncture treatments will consist of 24 sessions, each lasting 30 minutes, and will be administered 3 times per week over 8 weeks. All other procedures will remain consistent with 4-week group. The differences and similarities between two groups are shown in Supplemental Table 1.

Outcomes

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If patients with unilateral osteoarthritis, the evaluation of outcomes will pertain exclusively to that knee. For bilateral osteoarthritis, the knee with worse symptoms at baseline will be assessed.

Primary outcome

The primary outcome is the response rate at week 26, which is defined as the proportion of patients achieving a minimal clinically important improvement (MCII)[42]. Specifically, the MCII is a ≥ 2-point improvement on the NRS and a ≥ 6-point improvement on the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) function score compared to baseline[42]. An 11-point NRS ranges from 'absence of pain' (0) to 'most intense pain imaginable' (10). The WOMAC function subscale scored from 0 to 68 will be used to evaluate the mean knee discomfort experienced over the preceding week, with lower scores indicating better functional ability.

Secondary outcomes

Response rate at other time points The response rate will be assessed at weeks 4, 8 and 16.

Knee-joint pain The mean pain experienced within the preceding week will be measured using an 11-point NRS and the WOMAC pain subscale at weeks 0, 4, 8, 16

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and 26. The WOMAC pain subscale spanning from 0 to 20 comprises 5 items[43]. Higher scores are indicative of increased pain.

Knee-joint function The average function of the last 7 days will be measured using the WOMAC function subscale at weeks 0, 4, 8, 16 and 26. The tool spans across a range of 0 to 68, encompassing 17 items. Lower scores on this subscale are indicative of superior physical function[43].

Knee-joint stiffness The mean stiffness throughout the preceding week will be assessed via the WOMAC stiffness subscale at weeks 0, 4, 8, 16 and 26. The WOMAC stiffness subscale ranges from 0 to 8, including 2 items, with higher scores indicating increased stiffness[43].

Quality of life The evaluation for the standard of living will be performed at weeks 0, 4, 8, 16 and 26, following the randomization process, by mean of the 12 item Short Form Health Survey (SF-12)[44]. The SF-12 comprises of both mental and physical domains, and each domain is calibrated from 0 to 100. Higher scores on the scale indicate an improved quality of life.

Patient global assessment The singular item of the patient global assessment concerns the knee symptoms experienced by participants during the preceding week. Utilizing the Visual Analogue Scale, which ranges from 0 to 100, the severity of the disease is

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positively correlated with the magnitude of the score. This inquiry will be administered at weeks 0, 4, 8, 16 and 26.

The Osteoarthritis Research Society International (OARSI) response rate The proportion of subjects with improvement in pain or function ≥ 50% and absolute change ≥20, or enhancement in a minimum of 2 of the following: pain ≥20% and absolute change ≥10, function ≥20% and absolute change ≥10, and patient's global assessment ≥20% and absolute change ≥10[45]. The OARSI response rate will be assessed at weeks 4, 8, 16 and 26.

Rescue medicine Any use of Diclofenac Sodium Enteric-coated Tables will be quantified at weeks 4, 8, 16 and 26.

Safety

For adverse events that occur during the trial, researchers should record the appearance time, duration, classification, severity, remedial actions taken, remedial process, final resolution, etc. on the case report form (CRF). Moreover, researchers will assess the correlation between the intervention and the adverse event, in conjunction with other potential causative and confounding factors, in a comprehensive manner. In the event of serious adverse occurrences, researchers should immediately address and report to the principal investigator. Adverse events comprise subcutaneous hematoma, unrelenting post-injection pain, pruritus at the needle puncture location, etc. It is

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imperative that all adverse events are meticulously tracked until resolution or stabilization is achieved.

Simple size

Drawing upon the team's prior research, the anticipated response rates for the 4-week and 8-week groups are 35% and 60%[30]. The sample size of 59 patients in each group was calculated to provide 80% power, with a two-tailed α level of 0.05, utilizing PASS15.05 software. This requires 74 patients per group allowing for 20% dropout.

Data analysis

Using IBM SPSS 26.0 software for statistical analysis, $P < 0.05$ will be deemed statistically significant. Measurement data will be tested for normality. For those conforming to a normal distribution, the mean and standard deviation will be calculated. For those that do not, median (interquartile range) will be calculated. And percentages will be used to enumeration data. All randomized cases will be included into intention-to-treat analysis, and missing data will be filled in using multiple imputation. Per protocol analysis will only include the cases that fully complied with the trial protocol and will be used for the primary outcome as sensitivity analysis. If measurement data conforms to a normal distribution, it will undergo *t*-test analysis. While it does not conform to normal distribution, it will be subjected to Mann-Whitney test. Enumeration data will be analyzed via χ^2 test or Fisher 's exact test. NRS and WOMAC scores at multiple time points will be compared using a mixed-effects model

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with repeated measure as sensitivity analysis. Subgroup analysis will be used for potential confounders such as age, gender and weight, and affected knee. Cost effectiveness of acupuncture will be assessed over 26 weeks in both 4-week and 8-week groups.

Data management

Data collector and entry clerks, data manager, statistician and outcome assessor will undergo training in data management. At the end of the treatment phase, all participant data will be completed and recorded on the original CRFs. The data will be entered into Excel spreadsheets by the data entry clerks in time, following which the accuracy of the 2 datasets will be compared by the data manager. Any discrepancies will be corrected in accordance with the original CRFs.

All paper files related to the research will be preserved, and electronic documents will be securely stored on a password-protected computer. These research documents, whether in paper or electronic form, will be retained for a minimum of 5 years following publication. If readers and reviewers have any questions regarding our published data, they can contact the corresponding author to request the original data. Patient private information, including their name and telephone number, will be safeguarded. The trial has a low risk of safety and is not designed for interim analyses. Therefore, Data Monitoring Committee will not be established.

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Quality control

Patients will be included in strict accordance with diagnosis, inclusion and exclusion criteria. Standard operating procedures was developed for each aspect of the trial to ensure uniformity in its implementation and provide a reference in case of disagreements. Researchers will undergo uniform training that cover the study objectives, treatment standards, random allocation, acupuncture techniques, and assessment forms. And they should strictly follow the subject design plan, fill in the CRF carefully and objectively, and record truthfully all kinds of problems that arise in the clinical trial. Compliance control will be reinforced by registering participants' contact information and then making an appointment in advance for them to come to the treatment. The inspector will regularly check the trial records. Any problems encountered will be reported to the supervisor promptly, and strict measures will be taken to identify and solve them. During the trial, various researchers will be responsible for the generation of the random number sequence, allocation concealment, patients' recruitment, acupuncture treatment and outcome measure assessment to control bias.

Ethics and dissemination

This protocol has been approved by the Medicial Ethical Committee of Beijing University of Chinese Medicine (2023BZYL0506) and registered on Chinese Clinical Trials Registry (ChiCTR2300073383). The participants' information will be kept anonymous and confidential. They can make the decision to withdraw from the trial at any time. All information will be encrypted and only the designated researcher can access to it. The study findings will be disseminated through presentation in a medical journal. Additionally, we plan to present them at select conferences and scientific meetings.

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Synthesis

Our clinical trial incorporates rigorous scientific methodologies and comprehensive outcome measures to assess treatment response, and we will provide a high-quality report on the difference in acupuncture treatment effect between 4 and 8 weeks. It is an innovative and practical approach, and the research will provide strong clinical evidence of effect of various acupuncture treatment courses. All participants will receive acupuncture treatment throughout the trial, without a placebo control group, which will promote their compliance.

These findings will enhance the high-quality evidence on the effect of different acupuncture treatment courses. Furthermore, this research will provide invaluable insights for developing effective and practical treatment plans for KOA patients. It will help make medical decisions, improve health insurance reimbursement programs, and ensure efficient allocation of precious healthcare resources.

Limitations

Firstly, the nature of the intervention and lack of completely inert sham needles precludes the possibility of blinding both acupuncturists and patients[46]. But data analysts and outcome assessors will be blinded, and acupuncturists will receive training on how to minimize bias by interacting less with patients. Sceondly, only patients with KL II or III will be included in this trial and results of the research will not be

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generalized to patients with KL IV, who might require longer treatment courses. Thirdly, the trial only compared two common treatment courses of acupuncture, 4 weeks and 8 weeks, without any comparison to other courses.

Trial status

This trial is currently recruiting participants.

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Authors' contributions

J-FT conceived the research. J-FT and YY initiated the research design. YY, J-FT, and C-ZL drafted and critically revised the manuscript for important intellectual content. X-ZW participated in methodological improvements of the protocol. Y-WX

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coordinated the study. C-ZL and Y-WX sought ethical approval. Y-MF assisted in manuscript revision. J-FT, C-ZL and B-HM sought funding. Y-MF and B-HM contributed significantly to the editing of this manuscript. All authors contributed to the refinement of the research protocol and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

References

1. Katz JN, Arant KR, Loeser RF. Diagnosis and Treatment of Hip and Knee Osteoarthritis: A Review. *JAMA* 2021;325(6):568-78. doi: 10.1001/jama.2020.22171
2. Hunter DJ, Bierma-Zeinstra S. Osteoarthritis. *Lancet* 2019;393(10182):1745-59. doi: 10.1016/S0140-6736(19)30417-9
3. Safiri S, Kolahi AA, Smith E, et al. Global, regional and national burden of osteoarthritis 1990-2017: a systematic analysis of the Global Burden of Disease Study 2017. *Ann Rheum Dis* 2020;79(6):819-28. doi: 10.1136/annrheumdis-2019-216515
4. Chen AT, Shrestha S, Collins JE, et al. Estimating contextual effect in nonpharmacological therapies for pain in knee osteoarthritis: a systematic analytic review. *Osteoarthritis Cartilage* 2020;28(9):1154-69. doi: 10.1016/j.joca.2020.05.007
5. Silverwood V, Blagojevic-Bucknall M, Jinks C, et al. Current evidence on risk factors for knee osteoarthritis in older adults: a systematic review and meta-analysis. *Osteoarthritis Cartilage* 2015;23(4):507-15. doi: 10.1016/j.joca.2014.11.019
6. Cross M, Smith E, Hoy D, et al. The global burden of hip and knee osteoarthritis: estimates from the global burden of disease 2010 study. *Ann Rheum Dis* 2014;73(7):1323-30. doi: 10.1136/annrheumdis-2013-204763
7. Hardenberg M, Spekle EM, Coenen P, et al. The economic burden of knee and hip osteoarthritis: absenteeism and costs in the Dutch workforce. *BMC Musculoskelet Disord* 2022;23(1):364. doi: 10.1186/s12891-022-05306-9
8. Nelson AE, Allen KD, Golightly YM, et al. A systematic review of recommendations and guidelines for the management of osteoarthritis: The chronic osteoarthritis management initiative of the U.S. bone and joint initiative. *Semin Arthritis Rheum* 2014;43(6):701-12. doi: 10.1016/j.semarthrit.2013.11.012
9. da Costa BR, Reichenbach S, Keller N, et al. Effectiveness of non-steroidal anti-inflammatory drugs for the treatment of pain in knee and hip osteoarthritis: a network meta-analysis. *Lancet* 2017;390(10090):e21-e33. doi: 10.1016/S0140-6736(17)31744-0
10. da Costa BR, Reichenbach S, Keller N, et al. RETRACTED: Effectiveness of non-steroidal anti-

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inflammatory drugs for the treatment of pain in knee and hip osteoarthritis: a network meta-analysis. *Lancet* 2016;387(10033):2093-105. doi: 10.1016/S0140-6736(16)30002-2

11. Juni P, Hari R, Rutjes AW, et al. Intra-articular corticosteroid for knee osteoarthritis. *Cochrane Database Syst Rev* 2015;2015(10):CD005328. doi: 10.1002/14651858.CD005328.pub3
12. Orchard JW. Is there a place for intra-articular corticosteroid injections in the treatment of knee osteoarthritis? *BMJ* 2020;368:l6923. doi: 10.1136/bmj.l6923
13. Cepeda MS, Camargo F, Zea C, et al. Tramadol for osteoarthritis: a systematic review and metaanalysis. *J Rheumatol* 2007;34(3):543-55
14. da Costa BR, Nuesch E, Kasteler R, et al. Oral or transdermal opioids for osteoarthritis of the knee or hip. *Cochrane Database Syst Rev* 2014(9):CD003115. doi: 10.1002/14651858.CD003115.pub4
15. da Costa BR, Pereira TV, Saadat P, et al. Effectiveness and safety of non-steroidal anti-inflammatory drugs and opioid treatment for knee and hip osteoarthritis: network meta-analysis. *BMJ* 2021;375:n2321. doi: 10.1136/bmj.n2321
16. Osani MC, Lohmander LS, Bannuru RR. Is There Any Role for Opioids in the Management of Knee and Hip Osteoarthritis? A Systematic Review and Meta-Analysis. *Arthritis Care Res (Hoboken)* 2021;73(10):1413-24. doi: 10.1002/acr.24363
17. Price AJ, Alvand A, Troelsen A, et al. Knee replacement. *Lancet* 2018;392(10158):1672-82. doi: 10.1016/S0140-6736(18)32344-4
18. Murray KE, Murray TE, O'Rourke AC, et al. Readability and Quality of Online Information on Osteoarthritis: An Objective Analysis With Historic Comparison. *Interact J Med Res* 2019;8(3):e12855. doi: 10.2196/12855
19. Dantas LO, Salvini TF, McAlindon TE. Knee osteoarthritis: key treatments and implications for physical therapy. *Braz J Phys Ther* 2021;25(2):135-46. doi: 10.1016/j.bjpt.2020.08.004
20. Kolasinski SL, Neogi T, Hochberg MC, et al. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Management of Osteoarthritis of the Hand, Hip, and Knee. *Arthritis Rheumatol* 2020;72(2):220-33. doi: 10.1002/art.41142
21. Hunter DJ, Harris RE. Acupuncture and Knee Osteoarthritis: Does Dose Matter? *Arthritis Rheumatol* 2021;73(3):371-73. doi: 10.1002/art.41583
22. Chon TY, Lee MC. Acupuncture. *Mayo Clin Proc* 2013;88(10):1141-6. doi: 10.1016/j.mayocp.2013.06.009
23. Witt CM, Reinhold T, Jena S, et al. Cost-effectiveness of acupuncture treatment in patients with headache. *Cephalalgia* 2008;28(4):334-45. doi: 10.1111/j.1468-2982.2007.01504.x
24. MacPherson H, Thomas K, Walters S, et al. The York acupuncture safety study: prospective survey of 34 000 treatments by traditional acupuncturists. *BMJ* 2001;323(7311):486-7. doi: 10.1136/bmj.323.7311.486
25. Vickers AJ, Vertosick EA, Lewith G, et al. Acupuncture for Chronic Pain: Update of an Individual Patient Data Meta-Analysis. *J Pain* 2018;19(5):455-74. doi: 10.1016/j.jpain.2017.11.005
26. Mei F, Yao M, Wang Y, et al. Acupuncture for knee osteoarthritis: A systematic review and meta-analysis. *J Evid Based Med* 2023;16(2):138-40. doi: 10.1111/jebm.12532
27. Brophy RH, Fillingham YA. AAOS Clinical Practice Guideline Summary: Management of Osteoarthritis of the Knee (Nonarthroplasty), Third Edition. *J Am Acad Orthop Surg* 2022;30(9):e721-e29. doi: 10.5435/JAAOS-D-21-01233
28. Sun N, Tu JF, Lin LL, et al. Correlation between acupuncture dose and effectiveness in the treatment of knee osteoarthritis: a systematic review. *Acupunct Med* 2019;37(5):261-67. doi:

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

10.1136/acupmed-2017-011608

29. Witt C, Brinkhaus B, Jena S, et al. Acupuncture in patients with osteoarthritis of the knee: a randomised trial. *Lancet* 2005;366(9480):136-43. doi: 10.1016/S0140-6736(05)66871-7
30. Tu JF, Yang JW, Shi GX, et al. Efficacy of Intensive Acupuncture Versus Sham Acupuncture in Knee Osteoarthritis: A Randomized Controlled Trial. *Arthritis Rheumatol* 2021;73(3):448-58. doi: 10.1002/art.41584
31. Chen N, Wang J, Mucelli A, et al. Electro-Acupuncture is Beneficial for Knee Osteoarthritis: The Evidence from Meta-Analysis of Randomized Controlled Trials. *Am J Chin Med* 2017;45(5):965-85. doi: 10.1142/S0192415X17500513
32. Chen Y, Jia YJ, Lu JH, et al. [Comparision of therapertic effect of different acupuncture methods for knee osteoarthritis]. *Zhen Ci Yan Jiu* 2020;45(7):569-73. doi: 10.13702/j.1000-0607.191015
33. Bao F, Zhang Y, Wu ZH, et al. [Efficacy observation on knee osteoarthritis treated with electroacupuncture and its influence on articular cartilage with T2 mapping]. *Zhongguo Zhen Jiu* 2013;33(3):193-7
34. Sangdee C, Teekachunhatean S, Sananpanich K, et al. Electroacupuncture versus diclofenac in symptomatic treatment of osteoarthritis of the knee: a randomized controlled trial. *BMC Complement Altern Med* 2002;2:3. doi: 10.1186/1472-6882-2-3
35. Huang DE, Qin Y, Lin MN, et al. [Clinical efficacy of different waves of electroacupuncture on knee osteoarthritis and its effect on TGF-beta1 in joint fluid]. *Zhongguo Zhen Jiu* 2020;40(4):370-4. doi: 10.13703/j.0255-2930.20190422-0005
36. Lu N, Cheng P, Xia JX, et al. [Effect of acupuncture combined with moxibustion on serum matrix metalloproteinase-9 and matrix metalloproteinase inhibitor-1 in patients with knee osteoarthritis]. *Zhen Ci Yan Jiu* 2022;47(3):262-7. doi: 10.10372/j.1000-0607.20210079
37. Luo X, Liu J, Li Q, et al. Acupuncture for treatment of knee osteoarthritis: A clinical practice guideline. *J Evid Based Med* 2023;16(2):237-45. doi: 10.1111/jebm.12526
38. Yu Y KS, Tu JF, et al. Effect of acupuncture duration in patients with knee osteoarthritis: A secondary analysis of a multi-center randomized controlled trial. *World J Acupunct Moxibustion* 2023. doi: 10.1016/j.wjam.2023.10.004
39. Chan AW, Tetzlaff JM, Altman DG, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. *Ann Intern Med* 2013;158(3):200-7. doi: 10.7326/0003-4819-158-3-201302050-00583
40. Hochberg MC, Altman RD, Brandt KD, et al. Guidelines for the medical management of osteoarthritis. Part II. Osteoarthritis of the knee. American College of Rheumatology. *Arthritis Rheum* 1995;38(11):1541-6. doi: 10.1002/art.1780381104
41. Jensen MP, Karoly P, Braver S. The measurement of clinical pain intensity: a comparison of six methods. *Pain* 1986;27(1):117-26. doi: 10.1016/0304-3959(86)90228-9
42. Tubach F, Ravaud P, Baron G, et al. Evaluation of clinically relevant changes in patient reported outcomes in knee and hip osteoarthritis: the minimal clinically important improvement. *Ann Rheum Dis* 2005;64(1):29-33. doi: 10.1136/ard.2004.022905
43. Bellamy N, Buchanan WW, Goldsmith CH, et al. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. *J Rheumatol* 1988;15(12):1833-40
44. Ware J, Jr., Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. *Med Care* 1996;34(3):220-33. doi:

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

10.1097/00005650-199603000-00003

45. Pham T, Van Der Heijde D, Lassere M, et al. Outcome variables for osteoarthritis clinical trials: The OMERACT-OARSI set of responder criteria. *J Rheumatol* 2003;30(7):1648-54

46. Lee B, Kim TH, Birch S, et al. Comparative effectiveness of acupuncture in sham-controlled trials for knee osteoarthritis: A systematic review and network meta-analysis. *Front Med (Lausanne)* 2022;9:1061878. doi: 10.3389/fmed.2022.1061878

Figure legends

Figure 1 The schedule of assessments

NRS: numerical rating scale, WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index, SF-12: 12 item Short Form Health Survey, OARSI: Osteoarthritis Research Society International

Figure 2 The flow diagram of the trial

KOA: knee osteoarthritis

Figure 3 Meridian acupoints chart

Red points: obligatory acupoints; blue points: foot yangming meridian syndrome; purple points: foot shaoyang meridian syndrome; yellow points: foot taiyang meridian syndrome; green points: foot three-yin meridian syndrome

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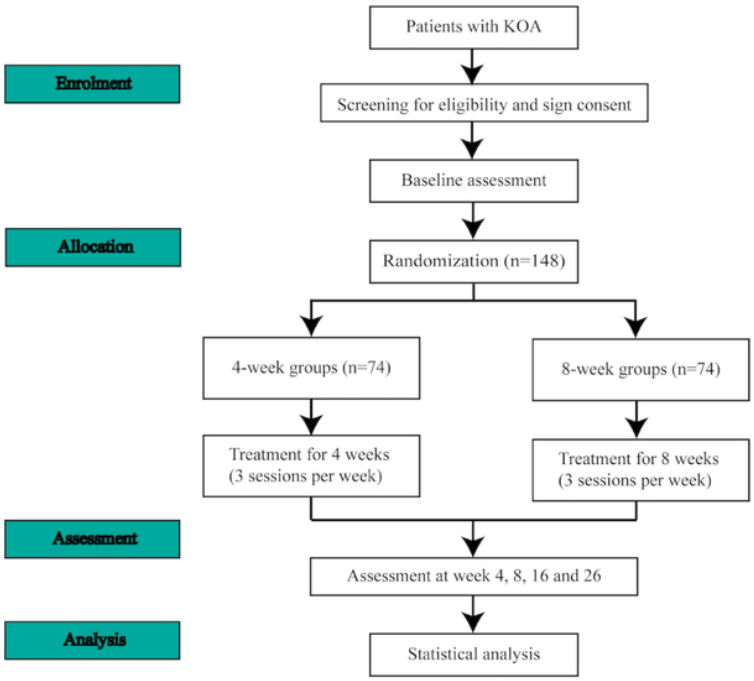
	Study period					
	Enrollment	Allocation	Postallocation			Closeout
Time point	Week -1	Week 0	Week 4	Week 8	Week 16	Week 26
Enrollment:						
Eligibility screen	×					
Informed consent	×					
Allocation		×				
Interventions:						
4-week group			⟷			
8-week group			⟷	⟷		
Assessment:						
Response rate			×	×	×	×
NRS	×		×	×	×	×
WOAMC	×		×	×	×	×
SF-12	×		×	×	×	×
Patient global assessment	×		×	×	×	×
The OARSI response rate			×	×	×	×
Rescue medicine			×	×	×	×
Adverse events			×	×	×	×

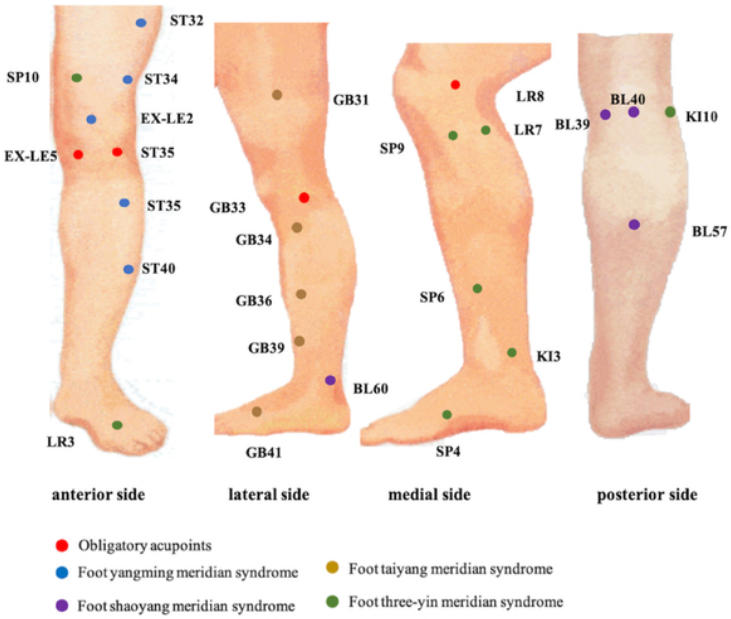
NRS: numerical rating scale, WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index, SF-12: 12 item Short Form Health Survey, OARSI: Osteoarthritis Research Society International

38x21mm (600 x 600 DPI)



KOA: knee osteoarthritis

34x25mm (600 x 600 DPI)



Red points: obligatory acupoints; blue points: foot yangming meridian syndrome; purple points: foot shaoyang meridian syndrome; yellow points: foot taiyang meridian syndrome; green points: foot three-yin meridian syndrome

33x20mm (600 x 600 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Page
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	5-16
Protocol version	3	Date and version identifier	3
Funding	4	Sources and types of financial, material, and other support	20
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1-2,21
	5b	Name and contact information for the trial sponsor	20
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	20
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	15-16

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*(continued)

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Section/item	Item No	Description	Page
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5-6
	6b	Explanation for choice of comparators	5-6,18
Objectives	7	Specific objectives or hypotheses	6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6-7
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7-8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9-12
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	Not applicable

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*(continued)

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Section/item	Item No	Description	Page
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	9
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	9
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	12-15
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	6-7, Figure 1, Table 4
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	16-17
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	7
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	8-9

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*(continued)

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Section/item	Item No	Description	Page
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	8-9
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8-9
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	9
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	9
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	15-16
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	15-16
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	15-16
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	17-18

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*(continued)

Section/item	Item No	Description	Page
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	17-18
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	17-18
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	16
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	Not applicable
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	15
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	15-16
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	21
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	Not applicable

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*(continued)

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Section/item	Item No	Description	Page
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Not applicable
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	15
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	21-22
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	20-21
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	Not applicable
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	20-21
	31b	Authorship eligibility guidelines and any intended use of professional writers	20-21
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Not applicable

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*(continued)

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Section/item	Item No	Description	Page
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	supplementary file
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Not applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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Supplemental Table 1 Differences and similarities for 4-week group and 8-week group

	4-week group	8-week group
Course	4 weeks	8 weeks
Session	12 sessions	24 sessions
Frequency	3 times per week	3 times per week
Duration	30 minutes each	30 minutes each
Acupoint	5 essential acupoints and 3 adjunct acupoints	5 essential acupoints and 3 adjunct acupoints
EA stimulation	a dilatation wave of 2/100 Hz	a dilatation wave of 2/100 Hz

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BMJ Open

Effect of 4 weeks versus 8 weeks of acupuncture for knee osteoarthritis in China: protocol for a randomized controlled trial

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Manuscripts

Effect of 4 weeks versus 8 weeks of acupuncture for knee osteoarthritis in China: protocol for a randomized controlled trial

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Abstract

Introduction Knee osteoarthritis represents the prevalent and incapacitating disease. Acupuncture, a widely used clinical treatment for knee osteoarthritis, has been shown to ameliorate pain and enhance joint function in affected individuals. However, there is a lack of evidence comparing different courses of acupuncture for knee osteoarthritis. In this trial, we will assess the effect of 4 weeks versus 8 weeks of acupuncture in patients with knee osteoarthritis.

Methods and analysis The protocol is a pragmatic, parallel, two-armed randomized controlled trial, with data analyst and assessor being blinded. 148 eligible patients with knee osteoarthritis will be randomly allocated in a 1:1 radio to receive 4-week or 8-week acupuncture. Electro-acupuncture will be administered 3 times per week for 4 or 8 weeks, respectively. Patients with knee osteoarthritis in both groups will be followed up to 26 weeks. The primary outcome is the response rate at week 26, and secondary outcomes include knee-joint pain, knee-joint function, knee-joint stiffness, quality of life, patient global assessment, the Osteoarthritis Research Society International response rate and rescue medicine. A cost-effectiveness analysis will be carried out over 26 weeks.

Ethics and dissemination The protocol has been approved by the Medical Ethical Committee of Beijing University of Chinese Medicine (2023BZYL0506). The study findings will be disseminated through presentation in a medical journal. Additionally, we plan to present them at selected conferences and scientific meetings.

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Trial registration The trial has been registered in the Chinese Clinical Trials Registry (ChiCTR2300073383. Register date: July 10, 2023, *https://www.chictr.org.cn/showproj.html?proj=199310*).

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Strengths and limitations of this study

1. Different courses of acupuncture for knee osteoarthritis will be head-to-head compared in this randomized controlled trial.
2. During the trial, various researchers will be responsible for the generation of the random number sequence, allocation concealment, patients' recruitment, acupuncture treatment and outcome measure assessment to control bias.
3. Cost effectiveness of acupuncture will be assessed over 26 weeks in both 4-week and 8-week groups.
4. The nature of the intervention precludes the possibility of blinding both acupuncturists and patients, which may bring bias.
5. The trial will only compare 2 common treatment courses of acupuncture, 4 weeks and 8 weeks, without any comparison to other courses.

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Background

Osteoarthritis, a degenerative joint disease, is a prevalent affliction among adults globally, with the knee joint being the most commonly affected [1, 2]. Estimates published in 2020 suggest that 300 million people worldwide are affected by hip and knee osteoarthritis (KOA) [3]. KOA is characterized by pain and functional limitations, which impairs patients' quality of life seriously [2, 4], with age, gender, obesity, excessive physical activities and previous knee trauma being some of the associated risk factors [1, 5]. Of note, female patients are more likely to suffer from KOA compared to males [1, 6]. And the incidence of KOA increases with age, making it a major contributor to disability in elderly population [1, 6]. The annual sick leave costs due to knee and hip osteoarthritis are about €40 million for the Dutch workforce, and KOA costs approximately twice as much as hip osteoarthritis [7]. KOA reduces the employability of patients and raises the cost of healthcare, which places a heavy financial burden on individuals and society.

Exercise therapy and weight loss have been shown to be effective in KOA [1], but sustained maintenance of these methods persists as a challenge [2] due to depending heavily on patient compliance [1]. Cognitive behavioral therapy may reduce pain of KOA patients, however, evidence is limited [8]. Acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs) are strongly recommended for KOA patients in the guideline [9]. Nonetheless, using acetaminophen alone is not much of a role [10]. Taking into consideration the potential gastrointestinal and cardiovascular side effect,

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NSAIDs should be used for shortest duration possible [11]. Intra-articular corticosteroid injections may be an effective management strategy for KOA patients, but prolonged usage increases the risk of joint deterioration [12, 13]. Opioid has limited benefits for KOA and a elevated risk of the gastrointestinal adverse event or somnolence [14, 15, 16, 17]. Over 20% of patients had a poor prognosis for knee replacement [18]. Despite this, the demand for this treatment continues to grow on a global scale, and young people account for an increasing proportion [18]. Opioid abuse and considerable growth for joint replacement requirements lead to overstretched healthcare systems. Urgent research is required to to develop new treatment options, evaluate the effect of existing treatments, or enhance current approaches [19].

As an integral component of the long-standing practice of traditional Chinese medicine spanning over 4000 years, acupuncture has emerged as a safe and low-risk physical therapy with demonstrated cost-effectiveness [19, 20, 21, 22]. Acupuncture is widely used in clinical practice to treating KOA, resulting in notable improvements in pain and joint function [19, 23, 24]. In light of these findings, the American College of Rheumatology and American Academy of Orthopaedic Surgeons have conditionally recommended the implementation of acupuncture for KOA [8, 25]. The effect of acupuncture is inherently intertwined with the treatment course [20, 26]. A cumulative course of treatment is required to produce and maintain the effect of acupuncture [20].

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Currently, there is a paucity of evidence about head-to-head comparison of diverse acupuncture courses, with regards to their effect in treating KOA. The 8-week acupuncture courses resulted in pain relief and improved joint function among KOA patients [27], which was consistent with our own previous research [28]. A meta-analysis has shown that a minimum of 4-week acupuncture treatment was needed to alleviate symptoms in KOA patients [29]. Additionally, other studies also have shown that 4-week acupuncture for KOA can conferred the relief patients' pain and dysfunction [30, 31, 32, 33, 34]. 4–8 weeks of acupuncture for KOA is recommended by the latest clinical practice guideline [35]. However, it is unclear which course of acupuncture is more effective, 8 weeks or 4 weeks for KOA [36]. More evidence is required to explain the effect of acupuncture for KOA between different treatment courses. In order to address this, we conduct a trial to evaluate the effect of 4 weeks versus 8 weeks of acupuncture for KOA.

Methods

Study design

This is a pragmatic, parallel, two-arm randomized controlled research scheduled to take place at Dongzhimen Hospital and Beijing Liangxiang Hospital from August 2023 to June 2024. A total of 148 eligible patients will be assigned randomly in a 1:1 radio to receive 4-week or 8-week acupuncture. Electro-acupuncture (EA) treatment will be administered 3 times per week for 4 or 8 weeks. KOA patients in both groups will be followed up to 26 weeks. The schedule of the assessments completed by all patients is

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illustrated in Figure 1 and the research flow diagram is presented in Figure 2. The protocol adheres to the principles of the Declaration of Helsinki and will be reported in accordance with the SPIRIT guidelines (additional file 1) [37].

Recruitment

Participants will be recruited from individuals diagnosed with KOA based on the American College of Rheumatology (ACR) criteria [38]. Announcements will be distributed through social media (WeChat), outpatient units and print advertisements. Interested patients can contact the clinical research coordinator (CRC) via telephone, e-mail, or WeChat to be enrolled in this research. The CRC will inform the study protocol in detail with them, including the purpose, procedures, time commitment, potential risks and benefits associated with participation in this trial. Following a preliminary screening process for inclusion and exclusion, potential candidates will be invited to undergo a face-to-face screening by CRC, who will advise patients to maintain their existing lifestyle. Confidentiality measures will be taken to safeguard patient privacy. Eligible participants will sign the informed consent before randomization.

Inclusion criteria

1. Aged 45-75 years (both genders).

2. Diagnosed with KOA according to the ACR criteria.

3. Unilateral/bilateral chronic knee pain for over 3 months.

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4. Radiologic confirmation of KOA within 6 months (Kellgren–Lawrence grade II or III).

5. The average score for knee pain during walking on flat ground in the last week ≥ 4 out of 10 on a numerical rating scale (NRS) [39].

6. Written informed consent.

Exclusion criteria

1. History of knee surgery or waiting for surgery (knee replacement or arthroscopic knee surgery).

2. Knee pain caused by other diseases (autoimmune diseases, infection, malignant tumours, trauma, fracture, joint loose bodies, severe effusion of joint cavity, lumbosacral vertebrae disease, gout, etc.).

3. Arthroscopy within 1 year and intra-articular injection in the past 6 months.

4. Acupuncture treatment during the past 6 months.

5. Serious acute or chronic organ diseases or mental disorders.

6. Blood coagulation disorders.

7. Pregnancy and breastfeeding.

8. Cardiac pacemaker and epilepsy.

9. Participation in another clinical study within 1 month.

Randomization

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All eligible patients will be randomly allocated to either 4-week group or 8-week group in a 1:1 ratio through a random number sequence, which will be generated by a professional statistician who is not involved in the assessment or treatment of participants using SAS 9.3 software. This trial will use stratified block randomisation, stratified by centre, with variable block length. The random number sequence and treatment plans will be placed inside corresponding numbered opaque envelopes. After the baseline assessment of eligible participants by CRC, an independent research assistant who is separate from the trial will assign the envelopes to acupuncturists. The acupuncturists will ensure the envelopes are sealed and will open them to determine which intervention should be performed. The CRC will be responsible for enrolling participants, obtaining informed consent and requesting randomization.

Blinding

In consideration of the nature of the intervention, the acupuncturists and patients will not be blinded. The outcome assessor and data analyst will be blinded to group assignments. The allocation will remain undisclosed to outcome assessor and data analyst until the completion of the statistical analysis.

Patient and public involvement

There is no patient or public involvement in study design, recruitment for or conduct of the study.

Interventions

The acupuncture prescription, derived from clinical practice and a pre-study [28], comprises 5 essential acupoints and 3 adjunct acupoints. The essential acupoints

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consist of dubi (ST35), neixiyan (EX-LE5), ququan (LR8), xiyangguan (GB33), and an ash point (the acupoint where the patient reports the most intense pain). The acupuncturist will select appropriate adjunct acupoints based on the patient's lesion types, which has been shown in Table 1. The acupoints are localized according to the World Health Organization Standard Acupuncture Locations and are presented in Table 2 and Figure 3. Licensed acupuncturists are of minimum 5 years' experience in acupuncture. For individuals afflicted with bilateral osteoarthritis, both knees will be subjected to acupuncture needling [27]. Conversely, unilateral osteoarthritis patient only receive acupuncture therapy on the affected knee [27]. Throughout the course of the trial, patients with pain unbearable can obtain Diclofenac Sodium Enteric-coated Tables (Beijing Novartis Pharma Ag) from the CRC, who will record the use of medication. Diclofenac Sodium Enteric-coated Tables will be dispensed in sets of 6 tablets, 25 mg per tablet, with instructions for patients to ingest one orally three times daily.

Table 1 The adjunct acupoints

Meridian syndrome	Acupoints
Foot yangming (anterior side of leg)	Liangqiu (ST34), zusanli (ST36), futu (ST32), fenglong (ST40), heding (EL-XE2)
Foot shaoyang (lateral side of the leg)	Fengshi (GB31), waiqiu (GB36), yanglingquan (GB34), xuanzhong (GB39), zulinqi (GB41)
Foot taiyang (posterior side of the leg)	Weiyang (BL39), weizhong (BL40), chengshan (BL57), kunlun(BL60)
Foot three-yin (medial side of the leg)	Xiguan (LR7), yinlingquan (SP9), xuehai (SP10), yingu (KI10), gongsun (SP4), sanyinjiao (SP6), taichong (LR3), taixi (KI3)

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Table 2 Acupoints manipulation

Acupoints	Angle	Depth	Twisting and reinforcing	De Qi
ST35	Oblique jab in the inner-up direction	0.5-1 inch	Even reinforcing-reducing	Yes
EX-LE5	Oblique jab in the external-superior directio	0.5-1 inch	Even reinforcing-reducing	Yes
LR8	Penetrating jab to GB33	1-1.5 inch	Reducing	Yes
GB33	Penetrating jab to LR8	1-1.5 inch	Reducing	Yes
GB34	Perpendicular inserting	1-1.5 inch	Even reinforcing-reducing	Yes
EX-LE2	Perpendicular inserting	0.8-1 inch	Even reinforcing-reducing	Yes
ST34	Perpendicular inserting	1-1.2 inch	Even reinforcing-reducing	Yes
ST36	Perpendicular inserting	1-2 inch	Reinforcing	Yes
ST40	Perpendicular inserting	1-1.5 inch	Reducing	Yes
ST32	Perpendicular inserting	1-2 inch	Reinforcing	Yes
GB31	Perpendicular inserting	1-1.5 inch	Reinforcing	Yes
GB36	Perpendicular inserting	0.5-0.8 inch	Even reinforcing-reducing	Yes
GB39	Perpendicular inserting	0.5-0.8 inch	Even reinforcing-reducing	Yes
GB41	Perpendicular inserting	0.5-0.8 inch	Even reinforcing-reducing	Yes
BL39	Perpendicular inserting	1-1.5 inch	reducing	Yes
BL40	Perpendicular inserting	1-1.5 inch	Even reinforcing-reducing	Yes
BL57	Perpendicular inserting	1.5-2 inch	Reinforcing	Yes
BL60	Perpendicular inserting	0.5-0.8 inch	Even reinforcing-reducing	Yes
KI3	Perpendicular inserting	0.5-0.8 inch	Reducing	Yes
KI10	Perpendicular inserting	1-1.5 inch	Even reinforcing-reducing	Yes
SP4	Perpendicular inserting	0.5-1.2 inch	Reducing	Yes
SP6	Perpendicular inserting	1-1.5 inch	Reinforcing	Yes
LR3	Perpendicular inserting	0.5-0.8 inch	Even reinforcing-reducing	Yes
LR7	Perpendicular inserting	1-1.5 inch	Even reinforcing-reducing	Yes
SP9	Perpendicular inserting	1.5-2 inch	Reducing	Yes
SP10	Perpendicular inserting	1-2 inch	Even reinforcing-reducing	Yes

Reinforcing: angle ＜90°, frequency ＞120r/min; Even reinforcing-reducing: angle between 120° and 180°, frequency between 60 and 120r/min; reducing: angle＞180°, frequency ＜ 60r/min

4-week group

Acupuncture treatments will consist of 12 sessions, each lasting 30 minutes, and will be administered 3 times per week over 4 weeks. Single-use aseptic needles (length: 25-40mm, diameter: 0.25mm, Hwato, Suzhou, China) will be used. Before needle insertion, both acupuncturist's hands and acupuncture site will be strictly disinfected

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with 75% alcohol. Then acupuncturists will proceed to apply the needles through the skin, selecting the appropriate acupuncture angle, depth, and manipulation technique as per Table 2. In order to achieve the sensation of "De Qi" (a composite sensation characterized by soreness, numbness, distention or heaviness), needles will be manually stimulated for a duration of 10s. Paired electrodes from an EA apparatus (HANS-200A acupoint nerve stimulator; Jisheng, Nanjing, China) will be attached to needle holders at LR 8-GB 33 and 2 adjunct acupoints. The electro-acupuncture stimulation will be a dilatation wave of 2/100 Hz, depending on the patient's comfort level.

8-week group

Acupuncture treatments will consist of 24 sessions, each lasting 30 minutes, and will be administered 3 times per week over 8 weeks. All other procedures will remain consistent with 4-week group. The differences and similarities between two groups are shown in Supplemental Table 1.

Outcomes

If patients with unilateral osteoarthritis, the evaluation of outcomes will pertain exclusively to that knee. For bilateral osteoarthritis, the knee with worse symptoms at baseline will be assessed.

Primary outcome

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The primary outcome is the response rate at week 26, which is defined as the proportion of patients achieving a minimal clinically important improvement (MCII) [40]. Specifically, the MCII is a ≥ 2-point improvement on the NRS and a ≥ 6-point improvement on the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) function score compared to baseline [40]. An 11-point NRS ranges from 'absence of pain' (0) to 'most intense pain imaginable' (10). The WOMAC function subscale scored from 0 to 68 will be used to evaluate the mean knee discomfort experienced over the preceding week, with lower scores indicating better functional ability.

Secondary outcomes

Response rate at other time points The response rate will be assessed at weeks 4, 8 and 16.

Knee-joint pain The mean pain experienced within the preceding week will be measured using an 11-point NRS and the WOMAC pain subscale at weeks 0, 4, 8, 16 and 26. The WOMAC pain subscale spanning from 0 to 20 comprises 5 items [41]. Higher scores are indicative of increased pain.

Knee-joint function The average function of the last 7 days will be measured using the WOMAC function subscale at weeks 0, 4, 8, 16 and 26. The tool spans across a range

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of 0 to 68, encompassing 17 items. Lower scores on this subscale are indicative of superior physical function [41].

Knee-joint stiffness The mean stiffness throughout the preceding week will be assessed via the WOMAC stiffness subscale at weeks 0, 4, 8, 16 and 26. The WOMAC stiffness subscale ranges from 0 to 8, including 2 items, with higher scores indicating increased stiffness [41].

Quality of life The evaluation for the standard of living will be performed at weeks 0, 4, 8, 16 and 26, following the randomization process, by mean of the 12 item Short Form Health Survey (SF-12) [42]. The SF-12 comprises of both mental and physical domains, and each domain is calibrated from 0 to 100. Higher scores on the scale indicate an improved quality of life.

Patient global assessment The singular item of the patient global assessment concerns the knee symptoms experienced by participants during the preceding week. Utilizing the Visual Analogue Scale, which ranges from 0 to 100, the severity of the disease is positively correlated with the magnitude of the score. This inquiry will be administered at weeks 0, 4, 8, 16 and 26.

The Osteoarthritis Research Society International (OARSI) response rate The proportion of subjects with improvement in pain or function ≥ 50% and absolute

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change ≥20, or enhancement in a minimum of 2 of the following: pain ≥20% and absolute change ≥10, function ≥20% and absolute change ≥10, and patient's global assessment ≥20% and absolute change ≥10 [43]. The OARSI response rate will be assessed at weeks 4, 8, 16 and 26.

Rescue medicine Any use of Diclofenac Sodium Enteric-coated Tables will be quantified at weeks 4, 8, 16 and 26.

Safety

For adverse events that occur during the trial, researchers should record the appearance time, duration, classification, severity, remedial actions taken, remedial process, final resolution, etc. on the case report form (CRF). Moreover, researchers will assess the correlation between the intervention and the adverse event, in conjunction with other potential causative and confounding factors, in a comprehensive manner. In the event of serious adverse occurrences, researchers should immediately address and report to the principal investigator. Adverse events comprise subcutaneous hematoma, unrelenting post-injection pain, pruritus at the needle puncture location, etc. It is imperative that all adverse events are meticulously tracked until resolution or stabilization is achieved.

Simple size

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Drawing upon the team's prior research, the anticipated response rates for the 4-week and 8-week groups are 35% and 60% [28]. The sample size of 59 patients in each group was calculated to provide 80% power, with a two-tailed α level of 0.05, utilizing PASS15.05 software. This requires 74 patients per group allowing for 20% dropout.

Data analysis

Using IBM SPSS 26.0 software for statistical analysis, $P < 0.05$ will be deemed statistically significant. Measurement data will be tested for normality. For those conforming to a normal distribution, the mean and standard deviation will be calculated. For those that do not, median (interquartile range) will be calculated. And percentages will be used to enumeration data. All randomized cases will be included into intention-to-treat analysis, and missing data will be filled in using multiple imputation. Per protocol analysis will only include the cases that fully complied with the trial protocol and will be used for the primary outcome as sensitivity analysis. If measurement data conforms to a normal distribution, it will undergo *t*-test analysis. While it does not conform to normal distribution, it will be subjected to Mann-Whitney test. Enumeration data will be analyzed via χ^2 test or Fisher 's exact test. NRS and WOMAC scores at multiple time points will be compared using a mixed-effects model with repeated measure as sensitivity analysis. Subgroup analysis will be used for potential confounders such as age, gender and weight, and affected knee. Cost effectiveness of acupuncture will be assessed over 26 weeks in both 4-week and 8-week groups.

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Data management

Data collector and entry clerks, data manager, statistician and outcome assessor will undergo training in data management. At the end of the treatment phase, all participant data will be completed and recorded on the original CRFs. The data will be entered into Excel spreadsheets by the data entry clerks in time, following which the accuracy of the 2 datasets will be compared by the data manager. Any discrepancies will be corrected in accordance with the original CRFs.

All paper files related to the research will be preserved, and electronic documents will be securely stored on a password-protected computer. These research documents, whether in paper or electronic form, will be retained for a minimum of 5 years following publication. If readers and reviewers have any questions regarding our published data, they can contact the corresponding author to request the original data. Patient private information, including their name and telephone number, will be safeguarded. The trial has a low risk of safety and is not designed for interim analyses. Therefore, Data Monitoring Committee will not be established.

Quality control

Patients will be included in strict accordance with diagnosis, inclusion and exclusion criteria. Standard operating procedures will be developed for each aspect of the trial to ensure uniformity in its implementation and provide a reference in case of disagreements. Researchers will undergo uniform training that covers the study

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objectives, treatment standards, random allocation, acupuncture techniques, and assessment forms. And they should strictly follow the subject design plan, fill in the CRF carefully and objectively, and record truthfully all kinds of problems that arise in the clinical trial. Compliance control will be reinforced by registering participants' contact information and then making an appointment in advance for them to come to the treatment. The inspector will regularly check the trial records. Any problems encountered will be reported to the supervisor promptly, and strict measures will be taken to identify and solve them. During the trial, various researchers will be responsible for the generation of the random number sequence, allocation concealment, patients' recruitment, acupuncture treatment and outcome measure assessment to control bias.

Ethics and dissemination

This protocol has been approved by the Medical Ethical Committee of Beijing University of Chinese Medicine (2023BZYL0506) and registered on Chinese Clinical Trials Registry (ChiCTR2300073383). The participants' information will be kept anonymous and confidential. They can make the decision to withdraw from the trial at any time. All information will be encrypted and only the designated researcher can access to it. The study findings will be disseminated through presentation in a medical journal. Additionally, we plan to present them at selected conferences and scientific meetings.

Synthesis

Our clinical trial incorporates rigorous scientific methodologies and comprehensive outcome measures to assess treatment response, and we will provide a high-quality

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report on the difference in acupuncture treatment effect between 4 and 8 weeks. It is an innovative and practical approach, and the research will provide strong clinical evidence of effect of various acupuncture treatment courses. All participants will receive acupuncture treatment throughout the trial, without a placebo control group, which will promote their compliance.

These findings will enhance the high-quality evidence on the effect of different acupuncture treatment courses. Furthermore, this research will provide invaluable insights for developing effective and practical treatment plans for KOA patients. It will help make medical decisions, improve health insurance reimbursement programs, and ensure efficient allocation of precious healthcare resources.

Limitations

Firstly, the nature of the intervention and lack of completely inert sham needles preclude the possibility of blinding both acupuncturists and patients [44]. But data analysts and outcome assessors will be blinded, and acupuncturists will receive training on how to minimize bias by interacting less with patients. Secondly, only patients with KL II or III will be included in this trial and results of the research will not be generalized to patients with KL IV, who might require longer treatment courses. Thirdly, the trial will only compare two common treatment courses of acupuncture, 4 weeks and 8 weeks, without any comparison to other courses.

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Trial status

This trial is currently recruiting participants.

Acknowledgements

We appreciate the researchers and institutions who will collaborate in this study, as well as all participants who will cooperate with our research.

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Authors' contributions

J-FT conceived the research. J-FT and YY initiated the research design. YY, J-FT, and C-ZL drafted and critically revised the manuscript for important intellectual content. X-ZW participated in methodological improvements of the protocol. Y-WX coordinated the study. C-ZL and Y-WX sought ethical approval. Y-MF assisted in manuscript revision. J-FT, C-ZL and B-HM sought funding. Y-MF and B-HM contributed significantly to the editing of this manuscript. All authors contributed to the refinement of the research protocol and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

References

[1] Katz JN, Arant KR, Loeser RF. Diagnosis and Treatment of Hip and Knee Osteoarthritis: A Review. *JAMA* 2021;325(6):568-78. doi: 10.1001/jama.2020.22171

[2] Hunter DJ, Bierma-Zeinstra S. Osteoarthritis. *Lancet* 2019;393(10182):1745-59. doi: 10.1016/S0140-6736(19)30417-9

[3] Safiri S, Kolahi AA, Smith E, et al. Global, regional and national burden of osteoarthritis 1990-2017: a systematic analysis of the Global Burden of Disease Study 2017. *Ann Rheum Dis* 2020;79(6):819-28. doi: 10.1136/annrheumdis-2019-216515

[4] Chen AT, Shrestha S, Collins JE, et al. Estimating contextual effect in nonpharmacological therapies for pain in knee osteoarthritis: a systematic analytic review. *Osteoarthritis Cartilage* 2020;28(9):1154-69. doi: 10.1016/j.joca.2020.05.007

[5] Silverwood V, Blagojevic-Bucknall M, Jinks C, et al. Current evidence on risk factors for knee osteoarthritis in older adults: a systematic review and meta-analysis. *Osteoarthritis Cartilage* 2015;23(4):507-15. doi: 10.1016/j.joca.2014.11.019

[6] Cross M, Smith E, Hoy D, et al. The global burden of hip and knee osteoarthritis: estimates from the global burden of disease 2010 study. *Ann Rheum Dis* 2014;73(7):1323-30. doi: 10.1136/annrheumdis-2013-204763

[7] Hardenberg M, Spekle EM, Coenen P, et al. The economic burden of knee and hip osteoarthritis: absenteeism and costs in the Dutch workforce. *BMC Musculoskelet Disord* 2022;23(1):364. doi: 10.1186/s12891-022-05306-9

[8] Kolasinski SL, Neogi T, Hochberg MC, et al. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Management of Osteoarthritis of the Hand, Hip, and Knee. *Arthritis Rheumatol* 2020;72(2):220-33. doi: 10.1002/art.41142

[9] Nelson AE, Allen KD, Golightly YM, et al. A systematic review of recommendations and guidelines for the management of osteoarthritis: The chronic osteoarthritis management initiative of the U.S. bone and joint initiative. *Semin Arthritis Rheum* 2014;43(6):701-12. doi: 10.1016/j.semarthrit.2013.11.012

[10] da Costa BR, Reichenbach S, Keller N, et al. Effectiveness of non-steroidal anti-inflammatory drugs for the treatment of pain in knee and hip osteoarthritis: a network meta-analysis. *Lancet* 2017;390(10090):e21-e33. doi: 10.1016/S0140-6736(17)31744-0

[11] da Costa BR, Reichenbach S, Keller N, et al. RETRACTED: Effectiveness of non-steroidal anti-inflammatory drugs for the treatment of pain in knee and hip osteoarthritis: a network meta-analysis. *Lancet* 2016;387(10033):2093-105. doi: 10.1016/S0140-6736(16)30002-2

[12] Juni P, Hari R, Rutjes AW, et al. Intra-articular corticosteroid for knee osteoarthritis. *Cochrane Database Syst Rev* 2015;2015(10):CD005328. doi: 10.1002/14651858.CD005328.pub3

[13] Orchard JW. Is there a place for intra-articular corticosteroid injections in the treatment of knee osteoarthritis? *BMJ* 2020;368:l6923. doi: 10.1136/bmj.l6923

[14] Cepeda MS, Camargo F, Zea C, et al. Tramadol for osteoarthritis: a systematic review and

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metaanalysis. *J Rheumatol* 2007;34(3):543-55

[15] da Costa BR, Nuesch E, Kasteler R, et al. Oral or transdermal opioids for osteoarthritis of the knee or hip. *Cochrane Database Syst Rev* 2014(9):CD003115. doi: 10.1002/14651858.CD003115.pub4

[16] da Costa BR, Pereira TV, Saadat P, et al. Effectiveness and safety of non-steroidal anti-inflammatory drugs and opioid treatment for knee and hip osteoarthritis: network meta-analysis. *BMJ* 2021;375:n2321. doi: 10.1136/bmj.n2321

[17] Osani MC, Lohmander LS, Bannuru RR. Is There Any Role for Opioids in the Management of Knee and Hip Osteoarthritis? A Systematic Review and Meta-Analysis. *Arthritis Care Res (Hoboken)* 2021;73(10):1413-24. doi: 10.1002/acr.24363

[18] Price AJ, Alvand A, Troelsen A, et al. Knee replacement. *Lancet* 2018;392(10158):1672-82. doi: 10.1016/S0140-6736(18)32344-4

[19] Hunter DJ, Harris RE. Acupuncture and Knee Osteoarthritis: Does Dose Matter? *Arthritis Rheumatol* 2021;73(3):371-73. doi: 10.1002/art.41583

[20] Chon TY, Lee MC. Acupuncture. *Mayo Clin Proc* 2013;88(10):1141-6. doi: 10.1016/j.mayocp.2013.06.009

[21] Witt CM, Reinhold T, Jena S, et al. Cost-effectiveness of acupuncture treatment in patients with headache. *Cephalalgia* 2008;28(4):334-45. doi: 10.1111/j.1468-2982.2007.01504.x

[22] MacPherson H, Thomas K, Walters S, et al. The York acupuncture safety study: prospective survey of 34 000 treatments by traditional acupuncturists. *BMJ* 2001;323(7311):486-7. doi: 10.1136/bmj.323.7311.486

[23] Vickers AJ, Vertosick EA, Lewith G, et al. Acupuncture for Chronic Pain: Update of an Individual Patient Data Meta-Analysis. *J Pain* 2018;19(5):455-74. doi: 10.1016/j.jpain.2017.11.005

[24] Mei F, Yao M, Wang Y, et al. Acupuncture for knee osteoarthritis: A systematic review and meta-analysis. *J Evid Based Med* 2023;16(2):138-40. doi: 10.1111/jebm.12532

[25] Brophy RH, Fillingham YA. AAOS Clinical Practice Guideline Summary: Management of Osteoarthritis of the Knee (Nonarthroplasty), Third Edition. *J Am Acad Orthop Surg* 2022;30(9):e721-e29. doi: 10.5435/JAAOS-D-21-01233

[26] Sun N, Tu JF, Lin LL, et al. Correlation between acupuncture dose and effectiveness in the treatment of knee osteoarthritis: a systematic review. *Acupunct Med* 2019;37(5):261-67. doi: 10.1136/acupmed-2017-011608

[27] Witt C, Brinkhaus B, Jena S, et al. Acupuncture in patients with osteoarthritis of the knee: a randomised trial. *Lancet* 2005;366(9480):136-43. doi: 10.1016/S0140-6736(05)66871-7

[28] Tu JF, Yang JW, Shi GX, et al. Efficacy of Intensive Acupuncture Versus Sham Acupuncture in Knee Osteoarthritis: A Randomized Controlled Trial. *Arthritis Rheumatol* 2021;73(3):448-58. doi: 10.1002/art.41584

[29] Chen N, Wang J, Mucelli A, et al. Electro-Acupuncture is Beneficial for Knee Osteoarthritis: The Evidence from Meta-Analysis of Randomized Controlled Trials. *Am J Chin Med* 2017;45(5):965-85. doi: 10.1142/S0192415X17500513

[30] Chen Y, Jia YJ, Lu JH, et al. [Comparision of therapertic effect of different acupuncture methods for knee osteoarthritis]. *Zhen Ci Yan Jiu* 2020;45(7):569-73. doi: 10.13702/j.1000-0607.191015

[31] Bao F, Zhang Y, Wu ZH, et al. [Efficacy observation on knee osteoarthritis treated with electroacupuncture and its influence on articular cartilage with T2 mapping]. *Zhongguo Zhen Jiu* 2013;33(3):193-7

[32] Sangdee C, Teekachunhatean S, Sananpanich K, et al. Electroacupuncture versus diclofenac in

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symptomatic treatment of osteoarthritis of the knee: a randomized controlled trial. *BMC Complement Altern Med* 2002;2:3. doi: 10.1186/1472-6882-2-3

[33] Huang DE, Qin Y, Lin MN, et al. [Clinical efficacy of different waves of electroacupuncture on knee osteoarthritis and its effect on TGF-beta1 in joint fluid]. *Zhongguo Zhen Jiu* 2020;40(4):370-4. doi: 10.13703/j.0255-2930.20190422-0005

[34] Lu N, Cheng P, Xia JX, et al. [Effect of acupuncture combined with moxibustion on serum matrix metalloproteinase-9 and matrix metalloproteinase inhibitor-1 in patients with knee osteoarthritis]. *Zhen Ci Yan Jiu* 2022;47(3):262-7. doi: 10.10372/j.1000-0607.20210079

[35] Luo X, Liu J, Li Q, et al. Acupuncture for treatment of knee osteoarthritis: A clinical practice guideline. *J Evid Based Med* 2023;16(2):237-45. doi: 10.1111/jebm.12526

[36] Yu Y, Kang SB, Tu JF, et al. Effect of acupuncture duration in patients with knee osteoarthritis: A secondary analysis of a multi-center randomized controlled trial. *World J Acupunct Moxibustion* 2023;33(4):372-6. doi: 10.1016/j.wjam.2023.10.004

[37] Chan AW, Tetzlaff JM, Altman DG, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. *Ann Intern Med* 2013;158(3):200-7. doi: 10.7326/0003-4819-158-3-201302050-00583

[38] Hochberg MC, Altman RD, Brandt KD, et al. Guidelines for the medical management of osteoarthritis. Part II. Osteoarthritis of the knee. American College of Rheumatology. *Arthritis Rheum* 1995;38(11):1541-6. doi: 10.1002/art.1780381104

[39] Jensen MP, Karoly P, Braver S. The measurement of clinical pain intensity: a comparison of six methods. *Pain* 1986;27(1):117-26. doi: 10.1016/0304-3959(86)90228-9

[40] Tubach F, Ravaud P, Baron G, et al. Evaluation of clinically relevant changes in patient reported outcomes in knee and hip osteoarthritis: the minimal clinically important improvement. *Ann Rheum Dis* 2005;64(1):29-33. doi: 10.1136/ard.2004.022905

[41] Bellamy N, Buchanan WW, Goldsmith CH, et al. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. *J Rheumatol* 1988;15(12):1833-40

[42] Ware J, Jr., Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. *Med Care* 1996;34(3):220-33. doi: 10.1097/00005650-199603000-00003

[43] Pham T, Van Der Heijde D, Lassere M, et al. Outcome variables for osteoarthritis clinical trials: The OMERACT-OARSI set of responder criteria. *J Rheumatol* 2003;30(7):1648-54

[44] Lee B, Kim TH, Birch S, et al. Comparative effectiveness of acupuncture in sham-controlled trials for knee osteoarthritis: A systematic review and network meta-analysis. *Front Med (Lausanne)* 2022;9:1061878. doi: 10.3389/fmed.2022.1061878

Figure legends

Figure 1 The schedule of assessments

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NRS: numerical rating scale, WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index, SF-12: 12 item Short Form Health Survey, OARSI: Osteoarthritis Research Society International

Figure 2 The flow diagram of the trial

KOA: knee osteoarthritis

Figure 3 Meridian acupoints chart

Red points: obligatory acupoints; blue points: foot yangming meridian syndrome; purple points: foot shaoyang meridian syndrome; yellow points: foot taiyang meridian syndrome; green points: foot three-yin meridian syndrome

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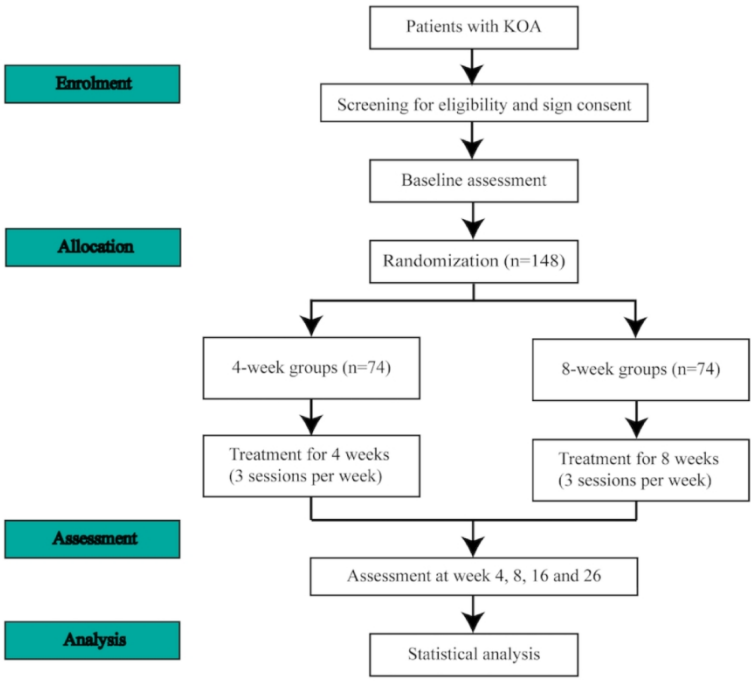
	Study period					
	Enrollment	Allocation	Postallocation			Closeout
Time point	Week -1	Week 0	Week 4	Week 8	Week 16	Week 26
Enrollment:						
Eligibility screen	×					
Informed consent	×					
Allocation		×				
Interventions:						
4-week group			⟷			
8-week group			⟷	⟷		
Assessment:						
Response rate			×	×	×	×
NRS	×		×	×	×	×
WOAMC	×		×	×	×	×
SF-12	×		×	×	×	×
Patient global assessment	×		×	×	×	×
The OARSI response rate			×	×	×	×
Rescue medicine			×	×	×	×
Adverse events			×	×	×	×

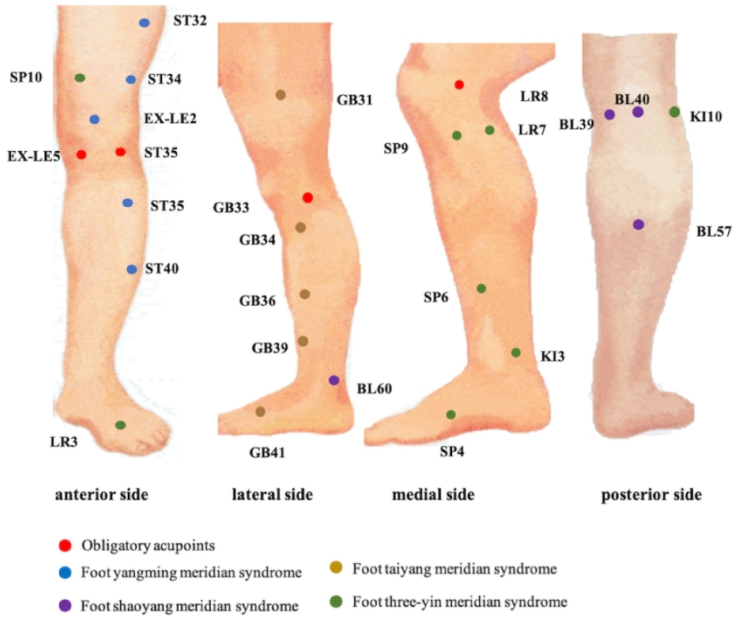
NRS: numerical rating scale, WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index, SF-12: 12 item Short Form Health Survey, OARSI: Osteoarthritis Research Society International

38x21mm (1200 x 1200 DPI)



KOA: knee osteoarthritis

34x25mm (1200 x 1200 DPI)



Red points: obligatory acupoints; blue points: foot yangming meridian syndrome; purple points: foot shaoyang meridian syndrome; yellow points: foot taiyang meridian syndrome; green points: foot three-yin meridian syndrome

33x20mm (1200 x 1200 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Page
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	5-16
Protocol version	3	Date and version identifier	3
Funding	4	Sources and types of financial, material, and other support	20
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1-2,21
	5b	Name and contact information for the trial sponsor	20
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	20
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	15-16

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*(continued)

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Section/item	Item No	Description	Page
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5-6
	6b	Explanation for choice of comparators	5-6,18
Objectives	7	Specific objectives or hypotheses	6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6-7
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7-8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9-12
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	Not applicable

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*(continued)

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Section/item	Item No	Description	Page
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	9
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	9
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	12-15
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	6-7, Figure 1, Table 4
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	16-17
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	7
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	8-9

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*(continued)

Section/item	Item No	Description	Page
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	8-9
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8-9
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	9
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	9
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	15-16
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	15-16
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	15-16
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	17-18

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*(continued)

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Section/item	Item No	Description	Page
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	17-18
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	17-18
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	16
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	Not applicable
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	15
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	15-16
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	21
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	Not applicable

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*(continued)

Section/item	Item No	Description	Page
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Not applicable
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	15
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	21-22
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	20-21
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	Not applicable
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	20-21
	31b	Authorship eligibility guidelines and any intended use of professional writers	20-21
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Not applicable

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*(continued)

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Section/item	Item No	Description	Page
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	supplementary file
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Not applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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Supplemental Table 1 Differences and similarities for 4-week group and 8-week group

	4-week group	8-week group
Course	4 weeks	8 weeks
Session	12 sessions	24 sessions
Frequency	3 times per week	3 times per week
Duration	30 minutes each	30 minutes each
Acupoint	5 essential acupoints and 3 adjunct acupoints	5 essential acupoints and 3 adjunct acupoints
EA stimulation	a dilatation wave of 2/100 Hz	a dilatation wave of 2/100 Hz

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