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# Pulsed electromagnetic fields for the management of knee osteoarthritis: multicentre, randomised, controlled, non-inferiority trial protocol

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## ABSTRACT

**Introduction** Pulsed electromagnetic field (PEMF) is an available treatment for knee osteoarthritis (KOA), which is the most common cause of pain and disability. Nonetheless, whether the clinical effects are like that of most used drugs is unclear. Thus, this study aims to determine the effect of PEMF on pain relief by comparing them with the positive drug (celecoxib). Furthermore, this clinical trial aims to evaluate the effect of PEMF on function and quality of life with a long-term follow-up.

**Methods and analysis** This two-armed, non-inferiority, randomised, controlled trial will be conducted in the outpatient physiatry/physiotherapy clinic or inpatient ward of 17 hospitals in China. A total of 428 individuals will be included who are more than 40 years of age with diagnosed KOA. The participants will be randomly allocated to the PEMF group: receiving a 6-week PEMF (15 Hz, 30 mT) at a frequency of 40 min per day, 5 days per week plus sham drug (n=214), or drug group: receiving a 6-week celecoxib 200 mg combined with sham PEMF (n=214). Clinical outcomes will be measured at baseline (T0), mid-term of intervention (T1), post-intervention (T2), 10, 18 and 30 weeks (T3–5) of follow-up after randomisation. The primary outcome will be the Western Ontario and McMaster Universities (WOMAC) pain index. The secondary outcomes will be WOMAC function and stiffness, pain measured by numerical rating score, quality of life, 6-minute walk test, pain catastrophising scale and responder index.

**Ethics and dissemination** The trial is performed following the Declaration of Helsinki. The study protocol and consent form have been approved by the Ethics Committee on Biomedical Research of West China Hospital of Sichuan University (#2021-220). All patients will give informed consent before participation and the trial is initiated after approval. Results of this trial will be disseminated through publication in peer-reviewed journals.

**Trial registration number** ChiCTR2100052131.

## STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study is a multicentre, parallel, prospective, randomised, non-inferiority study; all investigators are required to undertake mandatory training in the protocol.
⇒ This study sets up a specific parameter (pulse frequency, intensity and duration) for the pulsed electromagnetic field exposure.
⇒ A limitation is that this trial only set celecoxib as a positive control treatment, rather than a placebo.
⇒ There is a potential risk of unblinding by participants although researchers will ask participants not to share information among themselves and compare treatments received.

## INTRODUCTION

### Background and rationale

Osteoarthritis is a common and disabling condition that represents substantial health and socioeconomic costs with notable implications for the individuals affected and the healthcare systems.[1] It is estimated that approximately 1.71 billion people around the globe have musculoskeletal conditions, among which osteoarthritis accounted for 343 million, costing billions of dollars to economies annually.[2] The global percentage change of years lived with disability (YLDs) between 2006 and 2016 was 31.5%.[3] In China, around 61.2 million individuals with osteoarthritis were recorded in 2017.[4 5] The knee joint is the most prevalent subtype of osteoarthritis.[6] It is estimated that the total number of YLDs for knee osteoarthritis (KOA) reached to 4 149 628 in China, and the YLD rate as per 968 per million population, in which Southwest China had the highest YLD rate from KOA, accounted for 1653 per million population.[7]

The symptom relief with analgesics and non-steroidal anti-inflammatory drugs (NSAIDs) is the focus in the management of KOA, while serious gastrointestinal and cardiovascular adverse effects have been recorded.[8 9] Evidence-based guidelines

from Osteoarthritis Research International and American College of Rheumatology/Arthritis Foundation strongly recommend that non-pharmacological interventions focusing on the reduction of physical disability and impairment delivered in a multidisciplinary model should be optimal.[10 11] Although analgesics and NSAIDs remain the first-line treatment for KOA, there is an increasing need to develop non-pharmacological interventions so as to reduce costs of medication use and avoid side effects caused by the chronic use of medications like NSAIDs, particularly in the elderly population.[12] Among these available treatments, pulsed electromagnetic field (PEMF), generated by electrical current passing through external electromagnetic coils,[13] is a promising non-pharmacological, inexpensive and safe form of analgesia for KOA. Accumulating basic evidence suggests that preventing cartilage degeneration, maintaining subchondral microarchitecture and reducing synovitis are potential underlying mechanisms of PEMF in relieving pain and improving physical function for KOA.[14] PEMFs have been recognised by the European Alliance of Associations for Rheumatology[15] and Royal Dutch Society for Physical Therapy[16] as a potential treatment option for conditional use.

Nonetheless, data from systematic reviews and meta-analysis are contradictory. One systematic review reported that no significant beneficial effect on pain and physical function was found after 6 weeks of PEMF treatment.[17] Moreover, results from our review with nine included clinical trials involving 636 participants with KOA indicated that PEMF exposure may be effective in reducing pain but was found not significantly improving physical function and quality of life (QOL).[18] Further, we updated the results that PEMFs are beneficial in reducing stiffness and improving physical function in the short term, by adding 6 studies to a total of 15 involving 1078 participants based on the previous analysis.[19] Nonetheless, the other two studies reported that PEMFs were capable of improving physical function without exerting a positive effect on pain relief for KOA.[20 21] The discordant findings could be explained by involving different comparators, inconsistent parameters of PEMFs in the treatment algorithm (eg, frequency, intensity, treatment period, waveform and geometry), small sample sizes and without reporting outcome measures like responder index to reflect the clinical significance of PEMF treatment.[19]

PEMFs have been confirmed effective for reducing pain and improving function among individuals with KOA when compared with sham devices or placebo.[12 22–26] Nonetheless, PEMFs were used as an additional therapy to the NSAIDs in these studies.[12 22–26] In other words, the efficacy of PEMFs was widely proven as a combination with NSAIDs, while whether PEMF is effective without NSAIDs or not inferior to NSAIDs is not clear. Moreover, there was no consistent parameter among these studies that may be limited by the output of different devices. The effective intensity of PEMFs ranged from 0.001 to 105 mT, and the frequency ranged from 0.1 to 400 Hz.[19 21] To confirm the actual effect of PEMFs in the management of KOA, a positive controlled study with a large sample size, specific parameters and type of device, Outcome Measures in Rheumatology-Osteoarthritis Research Society International (OMERACT-OARSI) responder index, and long-term follow-up should be performed. If the PEMFs are found to be effective and non-inferior to active control, evidence generated from this study will inform decision-making in clinical practice employing PEMFs for the treatment of KOA with reduced intake of analgesics and NSAIDs.

### Objectives

#### Primary aim

The primary objectives are to confirm the effects of the 6-week PEMF pain in the management of KOA. The primary hypothesis is that PEMFs will result in non-inferior reductions in pain to celecoxib (drug group), which is recommended as the first-line analgesics by guidelines.[10 11]

#### Secondary aim

The secondary objectives are to confirm the effect of PEMFs on stiffness, physical function, QOL and walking ability, and to further confirm the long-term effects (24-week follow-up period after the intervention) with a large sample size and responder index. The secondary hypothesis: PEMFs will make non-inferior improvements in stiffness, function, QOL and walking ability to celecoxib, while with a more positive OMERACT-OARSI responder index. Moreover, the effects of PEMFs with a clinically significant difference will maintain over a 24-week follow-up.

## METHODS AND ANALYSES

### Study design

This study will be a non-inferiority, randomised controlled clinical trial with blinded assessment and a follow-up period of 6 months. The clinical trial began in October 2021, and participant enrolment will be completed in December 2022. This protocol has been designed according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement.[27] A completed SPIRIT checklist can be found in online supplemental material I. The study protocol has been registered at the Chinese Clinical Trial Registry (ChiCTR2100052131) and approved by the Ethics Committee on Biomedical Research of West China Hospital of Sichuan University.

### Study setting

The study will be conducted in 17 hospitals in China, including West China Hospital of Sichuan University, General Hospital of Ningxia Medical University, Second Hospital of Jilin University, First Affiliated Hospital of Zhengzhou University, Qinghai University Affiliated Hospital, Ganzi People's Hospital and others (seen in online supplemental material II).

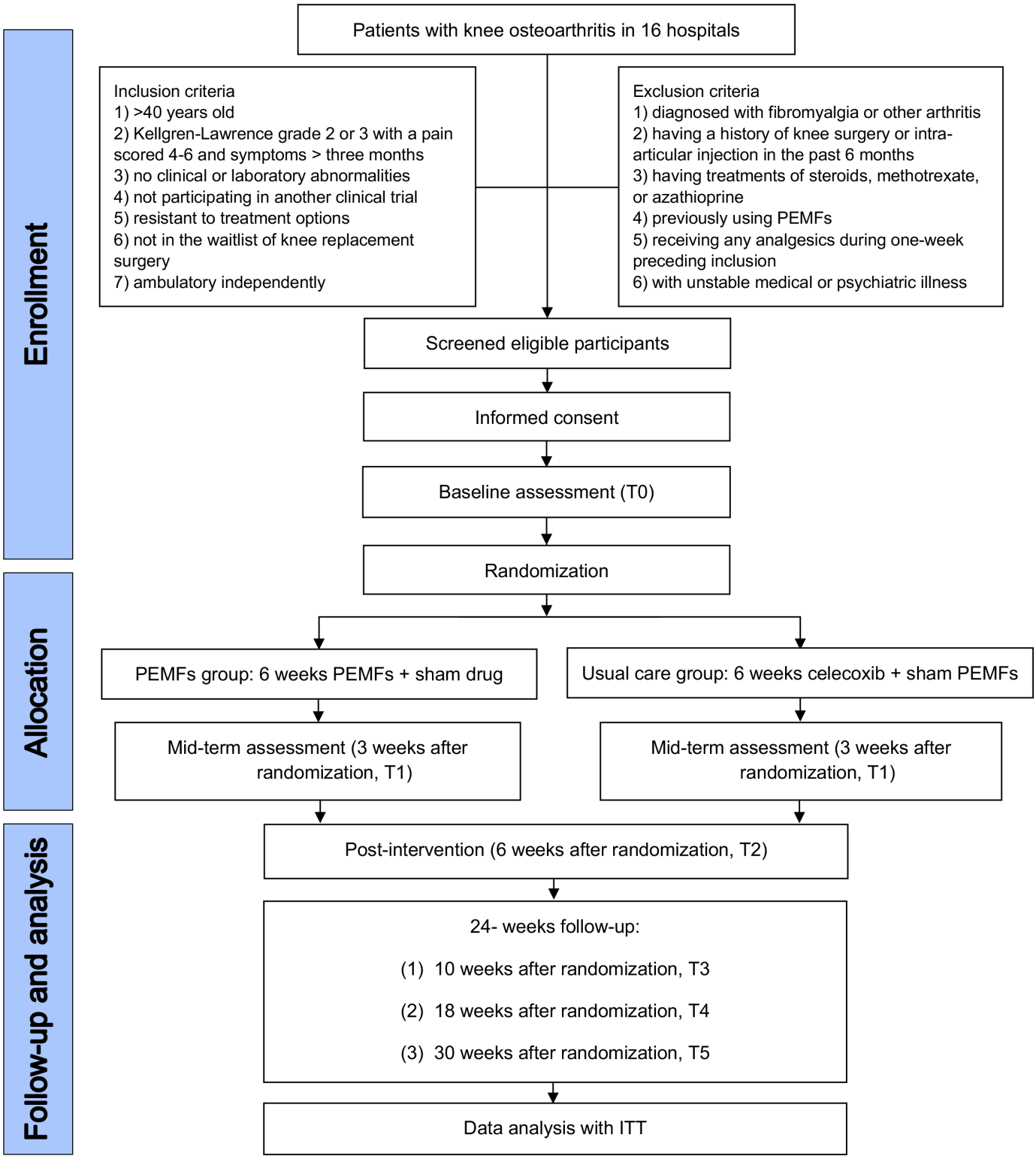


**Figure 1** Flow chart of the study. ITT, intention to treat; PEMFs, pulsed electromagnetic fields.

## Eligibility criteria

### Inclusion criteria

Participants diagnosed with KOA based on the 'Guidelines for the Diagnosis and Treatment of Osteoarthritis (2018 Edition)' by the Orthopaedic Branch of the Chinese Medical Association[28] and the diagnostic criteria for KOA formulated by the American College of Rheumatology in 2012[29] are eligible to participate when they meet the following criteria:

1. ≥40 years old.
2. Kellgren-Lawrence grade 2 or 3.[30]
3. With moderate knee pain between 4 and 6 on an 11-point numerical rating scale (NRS).
4. Having no obvious deformity.

5. Not participating in another clinical trial.
6. Resistant to treatment options involved in this trial including PEMFs, celecoxib or acetaminophen.
7. Not included in the waitlist for knee replacement surgery.
8. Ambulatory independently.

### Exclusion criteria

The exclusion criteria will be as follows:

1. Having other joint diseases, such as fraction, meniscal tear and so on.
2. Diagnosed with fibromyalgia or other arthritis, like rheumatoid arthritis or inflammatory arthritis.
3. Having a history of knee surgery or intra-articular injection in the past 6 months.
4. Previously using PEMFs in treating similar symptoms.
5. Receiving NSAIDs, opioids, amino acid glucose or any analgesics during 1 week preceding inclusion.
6. With any unstable medical or psychiatric illness.
7. Intolerant to analgesics such as acetaminophen and NSAIDs.

## Procedures

Individuals will be recruited from the outpatient physiatry/physiotherapy clinic or inpatient ward of 17 hospitals. All potential participants will be screened by a well-trained physical therapist at each site who is responsible for screening and blind to the allocation of the participants before entry into the study. At the same time, the general study process and the responsibilities of the participants and researchers will be explained to potential participants or their guardians. Individuals who understand the purposes and agree to participate will sign a written informed consent form according to the 1964 Declaration of Helsinki (seen in online supplemental material III). On the same day, the demographic data, anamnesis of KOA and related treatments (eg, age, gender, body mass index, comorbidities, duration of symptoms, previous treatment and surgery for KOA) will be recorded. After these, outcome measures at the baseline will be collected by two blinded researchers at each site (before randomisation, T0). During the trial, these two researchers will also collect the outcome data on the last day of the third week during the intervention (mid-term assessment, T1), the 6th week after randomisation (post-intervention assessment, T2), the 10th week (T3), 18th week (T4) and 30th week (T5) follow-up after randomisation. Figure 1 demonstrates the flow chart of the study.

## Interventions

All participants in both groups will be informed that they will not have any special feelings, such as pain, burning sensation, coldness, numbness and so on during the intervention of PEMFs whether the machine is working or not.[31] For ethical considerations, all participants will be allowed to take acetaminophen and topical diclofenac sodium gel with a maximal 3 g per day as rescue medication which needs to be recorded and will be banned at least 48 hours before clinical evaluation.

Before the intervention, all participants will be informed about the parameters used, potential concerns about the application of PEMFs for KOA and any questions regarding this device. In the treatment protocol, participants will be placed in a sitting or supine position on a treatment table and asked to flex the knee under which a pillow will be placed. Under sterile conditions and appropriate monitoring, the treatment coils of PEMFs then will be placed across the knee. The parameters setting and model of PEMFs used in the intervention group will not change during the study.

## Protocol for PEMF group

Participants in the PEMF group will be invited to use the PEMF device for 40 min per day, 5 days a week, for 6 weeks. The device is manufactured by Better Health Corporation, Sichuan, China,[32] and has been approved by the National Medical Products Administration (registration number, 20162090198) for use in the management of KOA (figure 2). The operating frequency is set between 10 and 30 Hz with a duty cycle between 50% and 70%. The overall power consumption of the device is 160 VA, and the peak output power is 50 W, which generates therapeutic PEMF with intensity reaching between 10 and 30 mT. The operating system of the device is controlled by a control panel with 27 or more models combining different parameters. Three pads where the fields will be generated are placed directly above the therapeutic site


**Figure 2** The pulsed electromagnetic field device: (A) device application diagram, (B) operating machine and (C) operating machine and three pads that generate fields above the therapeutic site. Figure is owned by Better Health Corporation, Sichuan, China.

**Table 1** Study assessments at specific time points

| Study period | Before intervention | | Intervention | End of intervention | | | |
|---|---|---|---|---|---|---|---|
| | Enrolment | Allocation | Mid-term | Post-intervention | Follow-up | | |
| | Eligibility screen | Admission day | 3 weeks after randomisation | 6 weeks after randomisation | 1 month (10 weeks after randomisation) | 3 months (18 weeks after randomisation) | 6 months (30 weeks after randomisation) |
| Time point | –T1 | T0 | T1 | T2 | T3 | T4 | T5 |
| **Enrolment** | | | | | | | |
| Eligibility screening | ○ | | | | | | |
| Informed consent | ○ | | | | | | |
| Baseline assessment | | ○ | | | | | |
| Allocation | | ○ | | | | | |
| **Interventions** | | | | | | | |
| PEMFs | | | ○ | | | | |
| Celecoxib | | | ○ | | | | |
| **Assessments** | | | | | | | |
| Demographic data | ○ | | | | | | |
| Primary outcomes | | | | | | | |
| WOMAC for pain | | ← | — | — | — | — | → |
| Secondary outcomes | | | | | | | |
| WOMAC for physical function | | ← | — | — | — | — | → |
| WOMAC for stiffness | | ← | — | — | — | — | → |
| NRS | | ← | — | — | — | — | → |
| SF-36 | | ← | — | — | — | — | → |
| 6MWT | | ← | — | — | — | — | → |
| Pain catastrophising scale | | ← | — | — | — | — | → |
| OMERACT-OARSI responder index | | ← | — | — | — | — | → |

6MWT, 6-minute walk test; NRS, numerical rating scale; OMERACT-OARSI, Outcome Measures in Rheumatology-Osteoarthritis Research Society International; PEMFs, pulsed electromagnetic fields; SF-36, 36-Item Short Form Survey; WOMAC, Western Ontario and McMaster Universities.

and transfer energy to the tissue. In this study, the model will be set at a model with an intensity of 30 mT and a frequency of 15 Hz for the treatment. Further, participants will be asked to take one placebo capsule every morning continuously for 6 weeks. To maintain the blind, placebo capsules have an identical appearance to the celecoxib.

## Protocol for drug group

Participants assigned to the drug group will undergo a similar protocol of PEMF treatment. To blind research personnel and participants, the sham PEMF device will be set to work for 30 s and then ramps down to no output model without cutting down the power and signal lighting. Additionally, participants in the drug group will receive celecoxib 200 mg every morning continuously for 6 weeks.

## Outcomes

### Participant timeline

Table 1 shows the assessments at each time point following the SPIRIT statement.[27] Outcome measures will be assessed at five time points after the baseline.

### Outcome measures

Primary outcome: self-reported knee pain using the Western Ontario and McMaster Universities (WOMAC) Index.[33]

The secondary outcomes are as follows:

1. Self-reported knee difficulty with physical function using the WOMAC Index.[33]
2. Self-reported knee stiffness using the WOMAC Index.[33]
3. Overall average knee pain intensity over the last 48 hours by an NRS with terminal descriptors of 'no pain' (recorded as 0) and 'maximal pain' (recorded as 10).[34]
4. The QOL is measured by the 36-Item Short Form Survey.[35]
5. The 6-minute walk test measures exercise tolerance and objective physical function. Tests will be performed indoors in accordance with the guidelines of the American Thoracic Society.[36] At the beginning and end of the test, clinical researchers will record the participant's heart rate and peripheral oxygen saturation. In addition, the level of effort at the end of the test will be reported by the rate of perceived exertion based on the Borg scale.[37]

6. Catastrophic thinking related to pain will be measured by the pain catastrophising scale[38] to reflect how individuals experience and manage pain, and analgesic medicine use will be recorded using a log sheet.
7. OMERACT-OARSI responder index presents the response of the participants to therapy based on the criteria.[35 39]
8. The rate of adverse effects. The process of every adverse effect will be recorded in detail, which includes its cause, therapeutical approaches, outcome and whether it is considered to be related to the intervention. If there is any adverse effect, researchers at the corresponding site will report to an independent data safety monitoring committee in the leading hospital (West China Hospital of Sichuan University) for further therapy and disposal.

### Data and sample collection

During the 6 weeks following the baseline assessment, research staff will contact participants in both groups weekly by telephone. Any inconvenience with the treatment received will be asked. Participants' demographic data, history of diseases and health behaviour information will also be collected. In the evaluation process, measures of recruitment rate, attendance, and follow-up rate will be monitored and recorded. Reasons for exclusions, declining participation and the dropout of participants will be noted throughout the trial. Any issues on difficulties and barriers to completing the trial will be recorded. During the trial, adverse events, medication and other healthcare concerns will be recorded using a log sheet.

## Randomisation and allocation

Eligible participants will be randomised with a one-to-one intervention allocation to the PEMFs or drug group after signing the informed consent form. Randomisation will be performed in the order of recruitment by block randomisation using a computer-generated random sequence operated at the Centre for Biostatistics, Design, Measurement, and Evaluation of West China Hospital, Sichuan University by a senior statistician. Random permuted blocks of sizes 4 or 6 will be employed to ensure participants are allocated to each group equally. The codes of allocation will be placed in numbered, sealed and opaque envelopes prepared by an external research coordinator not involved in the trial.

## Blinding

Researchers and coordinators conducting the evaluation and data collection, and statisticians will be blinded to allocation. The evaluators for outcome measures will be trained before recruitment and will be blinded to the allocation of participants to the groups. The study hypotheses will also be blinded to participants. The statistician will be blinded to the group allocation until completing the analyses.

## Data integrity and monitoring

For the validity and credibility of the execution of the trial, an independent data safety monitoring committee will be assembled. The independent data safety monitoring committee has been established consisting of a chairman, two independent statisticians and three medical specialists. The committee should be responsible for (1) monitoring individuals' safety in the trial; (2) adjudicating adverse events, serious adverse events and deaths, which include considering the relation to the intervention, making medical decisions and providing essential treatment until the patient is stable; (3) reviewing efficacy data at planned interim analyses (if required); and (4) reviewing patient recruitment and withdrawal. The trial may be stopped by the monitoring committee if any serious adverse event is identified. Once 50% of the sample size is reached, a data quality audit will be performed during the trial being conducted. Further, data will be stored in encrypted spreadsheets on secured servers hosted by the West China Hospital of Sichuan University, in which any potential risk of omissions and errors will be regularly scrutinised, and then exported to statistical software for analysis by a statistician blinded to group allocation. All data collected in this trial will be restricted to the principal investigator, specific members of the research team, and the independent data safety monitoring committee using the backend of the database or servers. Results of this trial will be presented at conferences and published in the form of peer-reviewed journal manuscripts. All researchers in this trial will be considered as coauthors of future publications according to their contributions. The protocol of this trial will be posted on the website of the clinical trials registrations and the Human Research Ethics Committee.

## Statistical methods

### Sample size

Sample size calculation was conducted based on the between-group difference on the WOMAC pain, using population means and an SD derived from similar studies to determine the minimal clinically important improvement.[9 12] Based on a power of 80% and a 5% significance level (one-sided test), a non-inferiority margin of −0.48 is chosen,[12 40] assuming the mean difference between groups is 0.89 with SD of changes from baseline of 6.6 and 2.8 for PEMFs and drug, respectively. Considering a dropout rate of 20%, a sample size of 214 per group (a total of 428 participants) is required. Calculations were performed with PASS V.15.0 (NCSS) using tests for means in a repeated measures design.

### Statistical analysis

Summary statistics will be calculated and reported in accordance with the Consolidated Standards of Reporting Trial (CONSORT). The baseline comparability between groups will be tested among descriptive characteristics, as well as baseline outcome measures. The per-protocol and intention-to-treat (ITT) analysis will be performed

by a blinded statistician. The per-protocol analysis will be primarily used. Based on OARSI guidelines,[41] non-inferiority will be investigated using the per-protocol dataset with the inclusion of those randomised participants who attended ≥3 visits after the baseline assessment. The ITT analysis will be considered as a sensitivity check on the primary analysis with the full analysis set and the missing data were supplemented with the last observation carried forward method.[42] Quantitative data will be expressed as the mean (SD), and percentages will be used to describe nominal data. The treatment effect will be evaluated by the change in the primary outcome between group analyses, using independent t-test or analysis of variance (ANOVA) or Wilcoxon rank-sum test for quantitative variables and the $\chi^2$ test or the Fisher's exact test to adjust for participants' demographic data, history of diseases and health behaviour information. Correlations between data on treatment effect and outcome measures will be analysed using linear regression analysis in both groups. Repeated measures were analysed using repeated measures ANOVA or generalised estimation equations. Where applicable, multiperspective qualitative research approaches (eg, grounded theory[43]) will be used to understand user experiences and engagement with the intervention. Constructivist grounded theory and a relational ethics lens will guide the plan for qualitative analysis. The QSR NVivo V.12 software will be used to organise and store the qualitative data. If there is some imbalanced factor, a stratified or multifactor analysis will be performed. A statistical analysis plan will be posted on a public data repository before analysis. The analysis will be completed by the statisticians in the independent data safety monitoring committee.

## Patient and public involvement

Patients and healthcare professionals were consulted at the design stage to confirm the potential impact of PEMFs or drugs; feedback from these patient consultations shaped the primary outcome and other aspects of the study. Additionally, an advisory committee has been installed from the start of the development of the project. The recruitment and conduct of the study will be performed by researchers at each site.

## Ethics and dissemination

### Ethics approval

The protocol with any modifications before implementation will be resubmitted to the Human Research Ethics Committee of West China Hospital, Sichuan University, and amendments to the protocol will be updated in the trial registries and outlined in the section of dissemination. The confidentiality and privacy of data retrieved from this trial will be protected in accordance with clinical research regulations developed by the National Health Commission and the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use.[44 45] The final report or any presentations of this trial will be presented as aggregated results in which individual participants will not be identifiable.

### Dissemination and data sharing

The study will be reported according to the CONSORT: Guidelines for Randomised Studies. The results of own data will be disseminated to participants through interviews held with nurses. The final manuscript will be completed by the first two authors and the authorship of the final manuscript will depend on the actual contribution. Study results will be distributed using a broad dissemination strategy, including oral presentations at international meetings and publications in peer-reviewed international journals.

### Trial status

The protocol version number and date: V.3.0, 31 March 2021. The study was conceived and designed in 2021. Enrolment began in October 2021 and is expected to end in December 2022. At the time of manuscript preparation, more than 200 subjects had been enrolled. Enrolment in this study was ongoing at the time of manuscript submission.

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**Contributors** Study design—X-NX, S-YZ, CH and LY. Writing—X-NX and S-YZ. Data analysis—H-ZL and W-JY. PEMF development—S-YZ, K-PS, X-YW, HW and CZ. Project administration—CH. All authors read and approved the final manuscript.

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**Competing interests** None declared.

**Patient and public involvement** Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

**Patient consent for publication** Parental/guardian consent obtained.

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# Supplemental Materials:

## Contents





Xiang X-N, *et al. BMJ Open* 2022; 12:e060350. doi: 10.1136/bmjopen-2021-060350

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

| Section/item | Item No | Description | Addressed on page number |
|---|---|---|---|
| **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 | 9 |
| | 2b | All items from the World Health Organization Trial Registration Data Set | 9 |
| Protocol version | 3 | Date and version identifier | 19 |
| Funding | 4 | Sources and types of financial, material, and other support | 22 |
| Roles and responsibilities | 5a | Names, affiliations, and roles of protocol contributors | 21 |
| | 5b | Name and contact information for the trial sponsor | NA |
| | 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 | 22 |

| | | | |
|---|---|---|---|
| | 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) | 16-17 |
| **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 | 6-7 |
| | 6b | Explanation for choice of comparators | 8 |
| Objectives | 7 | Specific objectives or hypotheses | 9 |
| 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) | 9 |
| **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 | 9 |
| 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) | 10 |
| Interventions | 11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered | 12-13 |

| | | | |
|---|---|---|---|
| | 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) | 12, 15 |
| | 11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) | NA |
| | 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial | NA |
| 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 | 14-15 |
| 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) | 12, table 1 |
| 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 | 17-18 |
| Recruitment | 15 | Strategies for achieving adequate participant enrolment to reach target sample size | 11 |

**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 | 16 |
| 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 | 16 |
| Implementation | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions | 16 |
| Blinding (masking) | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how | 16 |
| | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial | 16 |
| **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 |

| | | | |
|---|---|---|---|
| | 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 | N/A |
| 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 |
| 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 | 18-19 |
| | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses) | 19 |
| | 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) | 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 | 16 |
| 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 | 16 |
| Auditing | 23 | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor | 16 |
| **Ethics and dissemination** | | | |
| Research ethics approval | 24 | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval | 20 |
| 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) | 20 |
| Consent or assent | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) | 11 |
| | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable | N/A |
| 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 | 19 |
| Declaration of interests | 28 | Financial and other competing interests for principal investigators for the overall trial and each study site | 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 | 17 |
| 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 | N/A |
| 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 |
| | 31b | Authorship eligibility guidelines and any intended use of professional writers | 20 |
| | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code | N/A |
| **Appendices** | | | |
| Informed consent materials | 32 | Model consent form and other related documentation given to participants and authorised surrogates | Supplementary material III |
| 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 | N/A |

*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.

List of Sites in the Trial

| No. | Site |
|---|---|
| 1 | West China Hospital of Sichuan University |
| 2 | The Second Hospital of Jilin University |
| 3 | The Second Affiliated Hospital of Heilongjiang University of Chinese Medicine |
| 4 | General Hospital of Ningxia Medical University |
| 5 | Shanghai General Hospital |
| 6 | Zhongnan Hospital of Wuhan University |
| 7 | The First Affiliated Hospital of Xinjiang Medical University |
| 8 | Qinghai University Affiliated Hospital |
| 9 | The First Hospital of Longquanyi District of Chengdu |
| 10 | Mianzhu people's Hospital |
| 11 | Ya’an people's Hospital |
| 12 | Ganzi People's Hospital |
| 13 | Yibin City No. 2 People's Hospital |
| 14 | Mianyang Central Hospital |
| 15 | Nanjiang people's Hospital |
| 16 | Dechang people's Hospital |
| 17 | The First Affiliated Hospital of Zhengzhou University |

Version：V3.0 Date：29th, April 2021

# Patient Consent Form

Dear participant:

You are invited into the “Pulsed Electromagnetic Fields for the Management of Knee Osteoarthritis: Multicentre, Randomised, Controlled, Non-inferiority Trial” which has been approved by the ethics committee on biomedical research of West China Hospital of Sichuan University (#2021-220).

## 1. Why do we carry out this study?

Knee osteoarthritis (KOA) is the most common cause of pain and disability. Pulsed electromagnetic fields (PEMFs) is an available treatment. Nonetheless, the clinical effects are consistent. Thus, this study aims to determine the effect of PEMFs with specific parameters on pain relief and function improvement by comparing them with the positive control (celecoxib).

## 2. What do you need to do if you agree to participate in this study?

You will be randomly assigned to the PEMFs or usual care group. Patients in the PEMFs group will receive a 6-week PEMFs therapy, and these in the drug group will receive a 6-week Celebrex treatment. You will be required to complete the visit by telephone at baseline (before randomization), and at weeks 1, 3, 6, 10, 18, and 30 after enrolment.

## 3. These individuals are not suitable for participating in this trial, who:

a) be diagnosed with fibromyalgia or other arthritis, like rheumatoid arthritis or inflammatory arthritis.

b) have a history of knee surgery or intra-articular injection in the past 6 months.

c) have treatments of steroids, methotrexate, or azathioprine.

d) previously used PEMFs in treating similar symptoms.

e) received any analgesics during one-week preceding inclusion.

f) be with any unstable medical or psychiatric illness.

## 4. What are the potential risks and possible adverse events of participating in the study?

Potential risks: The treatment options may not alleviate your existing symptoms due to personal emotions, anxiety, and other risk factors, and may aggravate the anxiety symptoms or fear of the disease although they are based on evidence-based medical guidelines and previous research evidence.

Adverse events:

- ✧ Skin allergy symptoms due to personal constitution reasons or using the patch.
- ✧ Gastrointestinal discomfort due to taking pain relief drugs.

Risk prevention and disposal: Researchers and medical workers have medical qualifications and complete the standardized training. During this process, patients will be free of charge and will receive appropriate examination and treatment at belonging site if suffered adverse events.

## 5. What are benefits you can take from the study?

- ✧ Free visit and treatment.
- ✧ Improvement in symptoms.
- ✧ Reduction dependence on drugs and avoid side effects caused by medicine.

## 6. Are there any fees need to pay during the study?

Participant in this study is completely free of charge, and patients can receive a transportation subsidy of up to ¥400 with the ticket.

## 7. Is personal information confidential?

Your research data will be kept in the West China Hospital of Sichuan University, and your medical records will be accessible to researchers, research authorities, and ethics review committees. Any public reports on the findings of this study will not disclose your personal identity.

## 8. Must I participate in a study?

Participation in this study is completely voluntary, and you may refuse to participate in the study or withdraw from this study at any stage of the trial without discrimination or retaliation, and your medical treatment and rights will not be affected. If you decide to withdraw from this study, please contact your doctor for proper diagnosis and treatment of the disease.

## Patient Statement:

I have read the above presentation on this study, and my researchers have fully explained to me the purpose of this study, its operational process, and the possible risks and potential benefits of participating in this study and answered all my relevant questions.

I understand the purpose of this study and I am free to withdraw at any time without medical cares or legal rights being affected. I am voluntary to participate in this study.

I understand that results of my visits may be shared with the research team of West China Hospital of Sichuan University.

I agree to allow any information provided to be medical research upon the understanding that my identity will remain anonymous wherever possible.

| **Please indicate your wishes in the below scenarios:** | | |
|---|---|---|
| Please tick or initial yes or no: | Please tick ✓ or initial | |
| | YES | NO |
| I agree for my details to be shared and used in further research that be running by West China Hospital of Sichuan University | ☐ | ☐ |

Patient (to be completed by the patient):

Signature: _____

Name (block letters): _____

Date: _____

Phone: _____

Legal representative (block letters, if applicable): _____

Relationship with patient: _____

Witness (block letters, if applicable): _____

Date: _____

## Investigator Statement:

I have explained the request to the above-named patient, particularly, the ethical principles, risks, benefits, free, voluntariness and confidentiality that may arise from participating in this study. And he/she has indicated his/her willingness for participating in this study.

Signature: _____

Name (block letters):_____

Date:_____

Ethics Committee on Biomedical Research,

West China Hospital of Sichuan University

Tel: 028-85422654，028-85423237

(1 copy for patient; 1 held in patient notes, original stored in Investigator Site File)