BMJ Open

Feasibility and safety of combining repetitive transcranial magnetic stimulation and quadriceps strengthening exercise for chronic pain in knee osteoarthritis: a study protocol for a pilot randomised controlled trial

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To cite: Chang W-J, Adie S, Naylor JM, *et al*. Feasibility and safety of combining repetitive transcranial magnetic stimulation and quadriceps strengthening exercise for chronic pain in knee osteoarthritis: a study protocol for a pilot randomised controlled trial. *BMJ Open* 2022;**12**:e062577. doi:10.1136/bmjopen-2022-062577

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2022-062577).

Received 04 March 2022
Accepted 20 July 2022

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ABSTRACT

Introduction Knee osteoarthritis is a leading cause of disability, resulting in pain and reduced quality of life. Exercise is the cornerstone of conservative management but effects are, at best, moderate. Early evidence suggests that repetitive transcranial magnetic stimulation (rTMS) applied over the primary motor cortex (M1) may improve the effect of exercise in knee osteoarthritis. This pilot study aims to (1) determine the feasibility, safety and participant-rated response to an intervention adding M1 rTMS to exercise in knee osteoarthritis; (2) elucidate physiological mechanisms in response to the intervention; (3) provide data to conduct a sample size calculation for a fully powered trial.

Methods and analysis This is a pilot randomised, assessor-blind, therapist-blind and participant-blind, sham-controlled trial. Thirty individuals with painful knee osteoarthritis will be recruited and randomly allocated to receive either: (1) active rTMS+exercise or (2) sham rTMS+exercise intervention. Participants will receive 15 min of either active or sham rTMS immediately prior to 30 min of supervised muscle strengthening exercise (2×/week, 6 weeks) and complete unsupervised home exercises. Outcome measures of feasibility, safety, pain, function and physiological mechanisms will be assessed before and/or after the intervention. Feasibility and safety will be analysed using descriptive analysis. Within-group and between-group comparisons of pain and function will be conducted to examine trends of efficacy.

Ethics and dissemination This study has been approved by the University of New South Wales Human Research Ethics Committee (HC210954). All participants will provide written informed consent. The study results will be submitted for peer-reviewed publication.

Trial registration number ACTRN12621001712897p.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Randomised, assessor-blind, therapist-blind and participant-blind, sham-controlled study design.
⇒ Provide detailed methodology for collecting data on the feasibility, safety, analgesic effect and central mechanisms of combined repetitive transcranial magnetic stimulation and exercise therapy in knee osteoarthritis.
⇒ This proof-of-concept study is not powered to determine treatment efficacy.

INTRODUCTION

Knee osteoarthritis is a leading cause of global disease burden resulting in significant pain, and reduced quality of life.[1] It is estimated that 10% of people aged over 60 years experience knee osteoarthritis symptoms,[2] resulting in pain and impaired physical function.[3 4] Exercise is the cornerstone of conservative treatment for knee osteoarthritis and recommended by all international guidelines.[5] Although comparable to pharmacological treatments, the effects of exercise are at best, moderate, for pain and function, and small for quality of life.[5] To optimise patient outcomes, innovative treatments are needed to enhance the effects of exercise in knee osteoarthritis.

Knee osteoarthritis is a well-defined joint disorder, yet pain severity does not always correlate with structural changes observed on radiographs.[6–8] This discrepancy has been attributed to maladaptive changes of physiological mechanisms involved in central pain processing.[9] For example, ongoing nociceptive input from the affected joint and deficient endogenous pain inhibition are thought to increase neuronal excitability of central pain pathways (termed central sensitisation),[10] manifesting as pain hypersensitivity.[11] Furthermore, altered primary motor cortex

(M1) function has been implicated in the development of chronic pain as M1 plays an essential role in motor control and central pain processing.[12 13] For example, M1 organisational changes are associated with poor performance on knee movement tasks[14] and more severe pain is linked to reduced M1 intracortical excitability[15] in people with knee osteoarthritis. Additionally, quadriceps muscle weakness, a hallmark of knee osteoarthritis associated with pain and disability,[16] is associated with voluntary activation deficit, defined as a reduction in neural drive from the central nervous system to the muscles.[17] Reduced M1 excitability and voluntary activation deficit from M1, implicated in quadriceps muscle weakness,[18] may therefore contribute to pain and physical impairments in knee osteoarthritis. Thus, novel treatments simultaneously targeting these peripheral and central mechanisms could have a beneficial impact on pain and function in knee osteoarthritis.

Repetitive transcranial magnetic stimulation (rTMS), a safe, painless, non-invasive brain stimulation technique, has been used to alleviate chronic pain by inducing neuroplastic changes within M1. Neuroimaging evidence suggests that rTMS applied over M1 reduces pain by activating endogenous opioid systems of brain regions involved in pain processing.[19 20] rTMS modulates activity in both cortical and subcortical regions, either decreasing (inhibitory, low-frequency stimulation <1 Hz) or increasing (excitatory, high-frequency stimulation >5 Hz) cortical excitability.[21] High-frequency rTMS applied over M1 has been shown to produce superior analgesic effects to low-frequency rTMS in chronic pain populations.[22] Recent meta-analyses confirmed analgesic effects favouring high-frequency rTMS for short-term relief in chronic pain.[23] Although a case study reported positive effects on pain and function,[24] clinical trials of rTMS in knee osteoarthritis are absent.

Exercise is known to exert peripheral and central effects on pain. Peripherally, exercise improves muscle strength and coordination and proprioception to enhance control of the joint, therefore reducing nociceptive input from the affected knee.[25] Centrally, exercise activates opiodergic pathways and endogenous pain control.[26] Synergistic intervention simultaneously modulating peripheral (exercise), and central (rTMS and exercise) mechanisms of knee osteoarthritis could produce greater improvements in pain.[27] Thus, combining high-frequency rTMS over M1 and exercise has the potential to improve outcomes in knee osteoarthritis beyond what can be achieved with rTMS or exercise alone. Although pooled data from a recent meta-analysis in chronic pain showed a moderate reduction in pain severity favouring the combined rTMS and exercise intervention,[28] no study has investigated this intervention in knee osteoarthritis. A proof-of-concept study is needed to determine the feasibility, safety and participant-rated response to intervention and the effects of such an intervention on pain and central mechanisms.

The aims of this study are to (1) assess the feasibility, safety and perceived patient response to an intervention adding M1 rTMS to exercise in knee osteoarthritis; (2) elucidate physiological mechanisms in response to the intervention and (3) provide data to conduct a sample size calculation for a fully powered trial.

METHODS AND ANALYSIS

This protocol was prepared according to the Standard Protocol Items: Recommendations for Interventional Trials statement (online supplemental table S1).[29] The trial will be reported following the Consolidated Standards of Reporting Trials statement for non-pharmacological treatment,[30] the Template for Intervention Description and Replication checklist and guide[31] and Consensus on Exercise Reporting Template.[32] It has been prospectively registered with the Australian and New Zealand Clinical Trials Registry (ACTRN12621001712897p) (online supplemental table S2).

Trial design

We will conduct a pilot two-arm parallel-group design, assessor-blind, therapist-blind and participant-blind randomised controlled trial. The outcome measures will be assessed at baseline and on treatment completion (6 weeks postrandomisation). In addition, measures of pain and function will also be collected 3 months postintervention (figure 1).

Participants

Inclusion criteria for participants are: (1) individuals aged ≥50 years with knee osteoarthritis based on the American College of Rheumatology Clinical Criteria,[33] having at least one of the following items: stiffness <30 min, crepitus, bony tenderness, bony enlargement, no palpable warmth; (2) knee pain for ≥3 months and on most days of the past month; (3) average pain intensity ≥4 on an 11-point Numeric Rating Scale (NRS) in the past week. Exclusion criteria are: (1) previous knee joint replacement or high tibial osteotomy on the affected side; (2) knee surgery or joint injection in the past 6 months; (3) planned surgery in the next 9 months; (4) using oral corticosteroids currently or in the past 4 weeks; (5) confirmed diagnosis of systemic arthritis (ie, rheumatoid arthritis); (6) previous knee fracture or malignancy; (7) other conditions affecting lower limb function; (8) taking part in any knee strengthening exercise in the past 6 months; (9) any loss of sensation of the affected lower limb; (10) neurological or psychiatric disorders; (11) use of neuroactive drugs; (12) contraindications to TMS (ie, epilepsy, metal implant in the skull) based on the TMS safety screening questionnaire.[34 35]

Recruitment

Participants in the community in Sydney, Australia will be recruited from local arthritis support groups, social media platforms and healthcare providers (medical practitioners, rheumatologists, orthopaedic surgeons and physiotherapists). Potential participants will first

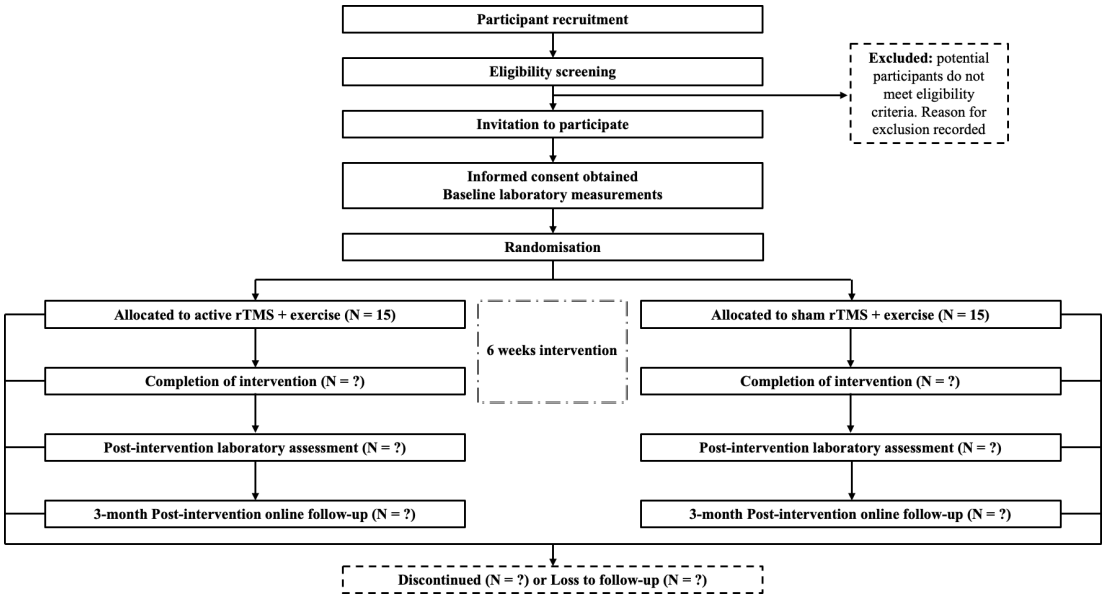

Figure 1 Study flow chart. rTMS, repetitive transcranial magnetic stimulation.

complete an eligibility screening questionnaire. Those who meet the eligibility criteria will be contacted by one of the researchers to confirm their willingness to participate in the study and to arrange the baseline assessment of outcomes. Participants will provide written informed consent to the outcome assessor on arrival for the baseline assessment.

Randomisation allocation concealment and blinding

Participants will be randomly allocated to either: (1) active rTMS+exercise or (2) sham rTMS+exercise, based on a 1:1 allocation ratio. The randomisation schedule will be generated by computer and a researcher not involved in recruitment, treatment provision or assessment. The randomisation schedule will be concealed in consecutively numbered, sealed opaque envelopes and given to the researcher who delivers rTMS intervention. Participants will be blinded to the type of rTMS they will receive and the study hypotheses. All participants will be given the same instructions and information about the rTMS intervention. Researchers conducting laboratory-based outcome assessment and physiotherapists providing exercise intervention will be blinded to group allocation. Unblinding will be allowed when an adverse or unexpected event occurs.

Outcome measurements

Measures of feasibility and safety

Feasibility and safety of the rTMS and exercise intervention will be assessed using the following measures: (1) the number of sessions attended by each participant (attendance rate >80% is considered feasible);[36] (2) the number of dropouts in each group (dropout rate <20% is considered feasible);[36] (3) the proportion of participants recruited from the total number screened; (4) willingness of each participant to undergo therapy at baseline on an 11-point NRS with 'not at all willing' at 0 and 'very willing' at 10 (80% of participants score 7 or more are considered feasible); (5) success of participant/outcome assessor/therapist blinding; (6) the number of adverse events and the details of each event.[27] Each adverse event will be considered separately. One or more serious adverse events will be considered unsafe. The success of participant blinding will be assessed at the completion of the intervention using a yes/no response to the question "Do you believe you received real brain stimulation?" and an 11-point NRS of the individual's confidence in that judgement. Participants will also be asked "Why do you believe you received the real/sham brain stimulation?" and "Was it divulged to you whether you were receiving real brain stimulation or not?"[27] Participant blinding will be considered successful if there is no difference between active rTMS+exercise and sham rTMS+exercise groups in the number of participants correctly guessing their treatment allocation at the completion of the follow-up laboratory assessment.[37] The success of blinding of the outcome assessor and treating physiotherapists will be determined at the completion of the follow-up assessment using a yes/no response to the question "Did you know which intervention group the participant was assigned to before completion of the follow-up laboratory assessment?" and "If you answer 'yes', how was it divulged to you?"[27] Blinding of the outcome assessor and treating physiotherapists will be considered successful if they answer 'no' to the first question.

Measures of pain and function

Knee pain and function will be assessed using: (1) an 11-point NRS for pain when walking in the past week;[38] (2) the Western Ontario and McMaster Universities Osteoarthritis Index (24 items, total score=96) (Likert V.3.1) and its pain subscale (7 items, total score=28) and physical function subscale (17 items, total score=68), a

valid, reliable and responsive instrument for knee osteoarthritis;[39] (3) the Global Perceived Effect Scale, where each participant will rate their perceived response to treatments on a 7-point Likert scale ranging from 'completely recovered' to 'vastly worsened';[40] (4) modified painDETECT questionnaire (7 items, total score=38), a simple, reliable and valid screening tool to detect a neuropathic pain component in patients with knee osteoarthritis;[41 42] (5) the number of painful sites, measured by participants indicating the number of painful sites outside of the affected knee lasting >24 hours in the past week on a four-sided body map (total score=35) with higher scores indicating more widespread hyperalgesia[43] and (6) the Pain Catastrophising Scale (13 items, total score=52), a reliable and valid, 13-item self-report instrument to assess patients' thoughts and feelings about pain in the domains of magnification, rumination and helplessness.[44]

To assess the long-term effects of the intervention, pain and function will also be assessed 3 months after the completion of intervention via an electronic version of these questionnaires.

Measures of physiological mechanisms

Measures of physiological mechanisms will be conducted in the same order for each participant.

1. M1 organisation and function will be measured using an established TMS mapping procedure.[45] Participants will be seated in a comfortable chair. Electromyography (EMG) of the quadriceps muscles will be recorded using bipolar surface electrodes (Ag-AgCl, Noraxon dual electrodes). The active electrode will be placed over the belly of the rectus femoris (RF), vastus lateralis (VL) and vastus medialis oblique (VMO) muscles and the ground electrode placed at the tibial shaft. EMG signals will be amplified (2000×) and filtered (20–1000 Hz), and digitally sampled at 2000 Hz using a Power 1902 Data Acquisition System and Spike2 software (CED, Cambridge, UK).

Single-pulse TMS delivered over M1 induces a magnetic field over the participant's scalp that evokes an electrical current in the underlying M1 tissue resulting in muscle activation recorded as motor evoked potentials (MEPs) using EMG. The scalp site evoking the largest MEP (termed the 'hotspot', the coil position inducing a maximal peak-to-peak MEP amplitude) for the RF muscle at a given TMS intensity will be identified.[46] The TMS motor threshold assessment tool will be used to determine the active motor threshold (aMT),[47] defined as the minimum intensity required to evoke a reliable MEP while participants maintained a muscle contraction of 10% averaged root mean square (RMS) EMG of three, 3 s maximal muscle contractions of the RF muscle.

During TMS mapping, 126 single-pulse biphasic stimuli (2 s interstimulus interval) will be delivered pseudorandomly to the scalp over a 6×7 cm (7 rows and 8 columns) grid oriented to the hotspot at 120% aMT of the RF muscle (Magstim Rapid^2/70 mm figure-of-eight coil; Magstim, UK). Participants will be asked to activate the RF muscle to 10% of their EMG recorded during a maximum voluntary contraction (determined as 10% of the highest RMS EMG for 1 s during three, 3 s maximal muscle contractions performed against manual resistance in sitting) with feedback provided on a monitor. The coil will be placed tangentially to the skull with the handle pointing laterally 90 degrees to induce a current in the lateral-to-medial direction. The Neural Navigator (Neurosoft, Russia) will be used to track the positions of the TMS coil and participant's head. To minimise muscle fatigue, stimuli will be delivered in trains of seven stimuli. The neuronavigational display is monitored to ensure adequate coverage of the grid and that adjacent positions not stimulated consecutively.

Maps for each of the RF, VL and VMO muscles will be produced offline using a custom MATLAB script (MathWorks, USA) according to previously published methods.[48 49] RMS amplitude of EMG traces of the MEPs will be extracted from a 20–50 ms window after stimulation and background RMS EMG (55–5 ms prior to stimulation) will be subtracted.[12 13] A surface map within a transformed plane encompassing stimulation coordinates and their corresponding MEP amplitude will be generated. The map will then be divided into 2744 partitions (49×56), with each partition assigned an estimated MEP amplitude based on the nearest acquired MEP values using triangular linear interpolation. Partitions with MEP amplitudes >10% of the maximum MEP amplitude will be considered as active.[48] Map volume is calculated as the sum of MEP amplitudes of all active partitions to index M1 corticomotor excitability.

2. Voluntary activation of the quadriceps muscles will be measured using a twitch interpolation technique when participants are seated with the hips and knees in 90 degrees flexion. A force increment will be recorded using a force transducer when an electrical stimulus delivered by a constant current stimulator (Digitimer, DS7AH) to the femoral nerve 1–2 s into the maximal muscle contraction (superimposed twitch), and again 3–4 s afterward when the muscles are at rest (control twitch). Voluntary activation (%)=[1−(superimposed twitch/control twitch)]×100.[50]
3. Pressure pain thresholds (PPTs) will be measured using a hand-held pressure algometer (Somedc, Hörby, Sweden, probe size 1 cm^2) to quantify mechanical sensitivity. The probe (size 1 cm^2) will be applied perpendicular to the skin (rate 40 kPa/s) until the participant first reports that the sensation of pressure has changed to pain. PPTs will be measured at the side of the knee joint line of the most painful knee and ipsilateral thumbnail. The average of three measurements at each site will be used in the analysis. PPT measures have been shown to be reliable in knee osteoarthritis (intraclass correlation coefficient (ICC)=0.83 (95% CI 0.72 to 0.90)).[51]
4. Conditioned pain modulation (CPM) is a well-established, reliable and safe measure of pain processing that is thought to reflect endogenous pain

inhibition. CPM is assessed as a change in the pain perceived in one body site (test stimulation) as a result of pain induced in another body site (conditioned stimulation). We will use PPT measured at the upper trapezius muscle contralateral to the painful knee as test stimulation[7] and pain is induced in the ipsilateral hand by cold pressor test (CPT) as conditioned stimulation. Three PPTs (test stimulation) will be measured before CPT (conditioned stimulation). For CPT, participants will immerse the hand in the cold water (4°C) for a maximum of 2 min.[52] Participants can remove their hand prior to the completion of CPT if the pain becomes unbearable and a pain rating on an NRS (0–100) will be obtained immediately after participants remove their hand. Three PPT measurements will then be repeated when pain score reaches 50 out of 100 after CPT. A reduction in PPT indicates deficient endogenous pain inhibition. CPM paradigm has shown good intrasession reliability (ICC >0.75).[53]

Intervention

Participants will be randomly allocated to either active rTMS+exercise or sham rTMS+exercise intervention groups. For participants with bilateral knee pain, the most painful knee or the right knee if both knees are equally painful, will be treated. All participants will receive a total of 12 treatment sessions (two sessions per week for 6 weeks). A systematic review recommended 12 supervised exercise sessions are needed to be effective for improving pain and disability in knee osteoarthritis.[54] Two qualified, registered physiotherapists with clinical experience in treating knee osteoarthritis will provide exercise therapy for all participants. A researcher trained in the use of rTMS will deliver active and sham rTMS to all participants according to their group allocation and will not be blinded to group allocation. Participants will be advised to continue with their usual medication during the study. Medications for their knee pain will be recorded at baseline and the follow-up laboratory assessment. Data for the frequency of use (in the past 6 months at baseline and during the 6-week intervention at follow-up) of pain medications will be collected. For each session, participants will receive active or sham rTMS (15 min) followed by supervised exercise (30 min).

Repetitive transcranial magnetic stimulation

For active rTMS, high-frequency rTMS will be applied to the motor hotspot of the first dorsal interosseous muscle ipsilateral to the treated knee using a Magstim Super Rapid^2 (Magstim) and a figure-of-eight air-cooled coil (70 mm). For each session, 3000 stimuli (10 Hz, 30 trains of 10 s, 20 s intertrain interval) will be delivered at 90% of resting motor threshold (rMT).[55] rMT is defined as the minimum intensity at which 5 out of 10 stimuli, delivered to the hotspot, evoked a peak-to-peak MEP of at least 50 µV.[46] To account for any between-session change in rMT, participants' rMT will be assessed at the beginning of each treatment session to determine the stimulation intensity.[56] For sham rTMS, a sham coil that looks identical to a real coil but produces only audible clicks and no magnetic pulse will be used to deliver the stimulation protocol identical to the one used for active rTMS. This is the most used sham rTMS protocol in controlled trials.[12 57 58]

Exercise

Immediately after the rTMS intervention, participants will receive one-to-one quadriceps strengthening exercise delivered by their treating physiotherapist. A standardised set of quadriceps strengthening exercises known to be effective in knee osteoarthritis will be performed using ankle cuff weights or resistance bands, and exercise intensity will be progressed by the physiotherapist as appropriate for each participant (online supplemental table S3).[5 25 59] A home exercise programme will also be developed and monitored by the physiotherapists for all participants to perform two times a week during intervention. Participants will complete an exercise diary and return to their treating physiotherapist weekly for compliance and adherence to their home exercise programme and for recording any adverse effects of home exercise (ie, whether pain was present, whether any exercises were difficult, the reason why exercises were unable to be completed if applicable).

Sample size and analysis

This is a pilot study designed to provide data to inform a full randomised controlled trial should the intervention appear feasible, safe and show trends of efficacy. Although a prospective sample size calculation is not required in a pilot randomised controlled trial, 15–20 participants per intervention group is recommended in pilot studies.[60 61] We have selected a sample size of 15 participants per group, or total 30 participants as this is achievable based on the successful completion of a previous pilot study with a similar design by our group.[27]

Measures of feasibility and safety will be analysed descriptively.[62] Within-group changes will be calculated as follow-up minus baseline (mean and SD). Two-sided t-tests will be used for within-group comparisons between baseline and follow-up measures and effect sizes will be calculated to indicate whether a full randomised controlled trial will be worthwhile. An effect size of 0.5 for pain and physical function outcomes is recommended for knee osteoarthritis clinical trials.[63] Due to the limitations of performing statistical comparisons with a small sample size and low power, statistical comparisons between groups will not be conducted.[64] Sample size calculation for a full randomised controlled trial will be based on the minimum clinically important difference (MCID) on outcome measures of pain and function.[64] The MCID in knee osteoarthritis studies is a change in pain of 1.8 unit (SD of 2.2) and a change in function of 6 units (SD of 9.7).[65] Power will be set at 80% to detect between-group differences, with an α of 0.05 and a dropout rate based on that of the pilot trial.

Patient and public involvement

We engaged a consumer representative form the Musculoskeletal Health Clinical Academic Group Consumer Community Council, Australian & New Zealand Musculoskeletal Clinical Trial Network and received feedback on the study including the proposed intervention and potential barriers to participant recruitment. The feedback from the consumer representative has been addressed and used to guide the design of intervention and recruitment strategies.

ETHICS, DATA SAFETY AND DISSEMINATION

This trial has been approved by the University of New South Wales Human Research Ethics Committee (HC210954), who may audit the study conduct during the study or after completion. Any deviation from protocol will require ethics amendment and be updated to the registry. This study will be terminated if any serious adverse event occurs. A serious adverse event is defined as any untoward medical occurrence or effect that results in death, or is life-threatening, requires hospitalisation, results in significant or persistent disability. There will not be a data monitoring committee due to the relatively short duration of this pilot study.

Participants' identifiers (ie, name, address, date of birth, sex, profession) will be removed from the data. Identifying information will be replaced with a unique anonymous identification number based on the recruitment order. Each participant will be assigned an anonymous identification number. This will be used in all further data recording and thus they will be de-identified. Paperwork that links anonymous identification number to participants' names will be stored in a locked room. All de-identified data that cannot be linked to an individual participant will be stored electronically with password protection. There is no perceived need to re-identify any electronic data. Only aggregate results will be reported; therefore, it will not be possible to identify individual participants in any information reported or published from this study. The data collected in hardcopy will be retained for 15 years after publication and electronic data will be stored for a minimum of 7 years.

Study results will be disseminated via presentations at scientific meetings and publications in a peer-reviewed journal. Publications and presentations related to this study will be authorised and reviewed by all study investigators.

Trial status

This trial will start recruiting in March 2022 and is expected to be completed by March 2023.

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Funding This work is supported by Australian & New Zealand Musculoskeletal Clinical Trial Network (Seed Granting Award).

Disclaimer The funding body does not have a role in study design and will not have a role in study execution, data analyses and interpretation or decision to submitting results.

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 and analysis' section for further details.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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APPENDIX - Supplementary Tables

Table S1. SPIRIT 2013 Checklist

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

Section/item	Item No	Description	Check/details
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	✓ Page 1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	✓ Page 7
	2b	All items from the World Health Organization Trial Registration Data Set	✓ Table 1
Protocol version	3	Date and version identifier	✓ Table 1
Funding	4	Sources and types of financial, material, and other support	✓ Page 18
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	✓ Page 1, 18
	5b	Name and contact information for the trial sponsor	✓ Table 1
	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	None

	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)	Not applicable
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	✓ Page 5-7
	6b	Explanation for choice of comparators	✓ Page 6
Objectives	7	Specific objectives or hypotheses	✓ Page 7
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)	✓ Page 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	✓ Page 8
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)	✓ Page 8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	✓ Page 14-15
	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)	✓ Page 17

	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	✓ Page 15
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	✓ Page 14
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	✓ Page 9-14
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)	✓ Figure 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	✓ Page 16
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	✓ Page 8
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	✓ Page 9
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	✓ Page 9
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	✓ Page 9

Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	✓ Page 9
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	✓ Page 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	✓ Page 9-14
	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	✓ Page 9-14
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	✓ Page 17
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	✓ Page 16
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	✓ Page 16
	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)	✓ Page 16
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	✓ Page 17

	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	✓ Page 17
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	✓ Page 9
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	✓ Page 17
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	✓ Page 17
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)	✓ Page 17
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	✓ Page 8
	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	✓ Page 17
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	✓ Page 18
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	✓ Approved by ethics committee
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	✓ Page 18
	31b	Authorship eligibility guidelines and any intended use of professional writers	✓ Page 18
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	✓ Page 17
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	✓ Approved by Ethics Committee
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.

TABLE S2. WHO trial registration data set (v.1.1)

Item	**Information**
Primary registry and trial identifying number	Australian and New Zealand Clinical Trials Registry (ACTRN12621001712897p)
Date of registration in primary registry	14 December 2021
Universal Trial Number	U1111-1274-6922
Source of monetary or material support	Australian & New Zealand Musculoskeletal Clinical Trial Network Seed Granting Award
Primary Sponsor	Neuroscience Research Australia
Contact for public queries	Dr Wei-Ju Chang, Neuroscience Research Australia [w.chang@neura.edu.au]
Contact for scientific queries	Dr Wei-Ju Chang, Neuroscience Research Australia
Public title	Non-invasive brain stimulation and exercise for treating knee osteoarthritis
Scientific title	Feasibility and safety of combining repetitive transcranial magnetic stimulation and quadriceps strengthening exercise for chronic pain in knee osteoarthritis – A pilot randomised controlled trial
Country of recruitment	Australia
Health condition or problem studies	Knee osteoarthritis
Interventions	Active treatment: Combined repetitive transcranial magnetic stimulation and quadriceps muscle strengthening exercise

	Control treatment: Combined sham repetitive transcranial magnetic stimulation and quadriceps muscle strengthening exercise
Key eligibility criteria	Inclusion criteria: 1. People aged ≥ 50 years with knee osteoarthritis based on the American College of Rheumatology Clinical Criteria 2. Knee pain for at least 3 months and on most days of the past month. 3. Average pain intensity equal or greater than 4 on an 11-point numeric rating scale in the past week.
	Exclusion criteria: 1. Previous knee joint replacement or high tibial osteotomy. 2. Knee surgery or joint injection in past six months. 3. Planned surgery in the next nine months. 4. Current or past four weeks oral corticosteroids use. 5. Systemic arthritis. 6. Previous knee fracture or malignancy. 7. Other condition affecting lower limb function. 8. Participation in knee strengthening exercise in past six months. 9. Loss of sensation of the affected lower limb. 10. Neurological or psychiatric disorders. 11. Use of neuroactive drugs. 12. Contraindications to transcranial magnetic stimulation
Study type	Interventional
	Purpose of study: treatment
	Allocation: 1:1 randomised controlled trial: Intervention assignment: parallel; Masking: participant-/therapist-/assessor-blinded

Date of the first enrolment	March 2022
Sample size	30
Recruitment status	Recruiting
Primary outcomes	Feasibility and safety (measured as the number of session attended, the number of drop-outs, proportion of participants recruited, willingness of each participant to undergo therapy, success of blinding, adverse events)
Secondary outcomes	Pain and function: numeric rating scale, WOMAC, Global Perceived Effect Scale, modified painDETECT, number of painful site, pain catastrophising scale. Physiological mechanisms: primary motor cortex organisation and function, voluntary activation of the quadriceps muscles, pressure pain thresholds, conditioned pain modulation.
Ethical review	Status: approved, Date of approval: 31 January 2022; Committee: UNSW Human Research Ethics Committee A (HC210954)

TABLE S3: The muscle strengthening exercise program with exercise description, progression and repetitions.

Exercise Description	Progression	Repetitions
1. Knee extensor strengthening Seated knee extensions with ankle weights. In a seated position, slowly straighten symptomatic knee until it is fully straight. Hold for 5 seconds and then lower slowly.	Ankle weights.	3 sets of 10. 30 second break period in between sets.
2. Hip abductor strengthening Level 1: Side lying hip abduction with ankle weights. Keep body still and knee straight and life affected leg up. Do not swing affected leg forward. Keep heel of foot higher than toes and behind hips while lifting straight upwards towards the ceiling. Hold for 5 seconds and then lower slowly.	Increase ankle weights or progress to level 2.	3 sets of 10. 30 second break period in between sets.
Level 2: Standing hip abduction with thera band/elastic resistance band. Place looped thera band/elastic resistance band around both legs just above the ankle. Adequate tension on the elastic band and correct upright posture with shoulders and hips both facing forward is required prior to starting the exercise. The back of a chair or a wall can be used to provide support. Hold for 5 seconds and then lower slowly.	Increase thera band/elastic band resistance.	3 sets of 10. 30 second break period in between sets.

Exercise Description	Progression	Repetitions
3. Weight-bearing knee/hip extensor strengthening Level 1: Partial wall squats (option shown is to add thera band/elastic band around knees to incorporate the hip abductor muscles). Stand with one foot 30cm away from the wall with feet apart and turned inwards. With back straight and trunk and buttocks against a wall, slowly slide down the wall (as if to sit) to approximately 60° (less if painful) and then back up again while keeping contact with the wall at all times. Knees must go past the toes during the squat exercise. Hold position for 5 seconds.	Increase resistance by adding thera band/elastic resistance band or if already in use increase elastic band resistance strength. Progress further to level 2.	3 sets of 10. 30 second break period in between sets.
Level 2: Sit-to-stand (option to add thera band/elastic band around knees to incorporate hip abductor muscles). Seated with back against a chair of standard height with firm seat, slowly stand up without using hands for support. Lean forward over toes so that the buttocks are lifted and hips go under the trunk. Hold for 3 seconds with buttocks slightly off the chair before sitting back down slowly.	Increase resistance by adding thera band/resistance elastic band. If already in use increase elastic band resistance strength. Progress further to level 3.	3 sets of 10. 30 second break period in between sets.
Level 3: Alternate split sit-to-stand Place the foot of the unaffected leg 10cm in front of the other foot.	Increase depth of squat.	3 sets of 10. 30 second break period in between sets.

Exercise Description	Progression	Repetitions
Slowly stand by leaning forward with back straight (nose in front of the toes) and squeeze buttock muscles. Most weight bearing must be on the symptomatic knee. Hold for 3 seconds with buttocks slightly off the chair before sitting back down slowly.		
Level 3+: Split partial wall squats Slowly slide down the wall (as if to sit) keeping the trunk and buttocks in contact with the wall. Knees must move over the toes. Most weight bearing must be on the symptomatic knee. Stop when symptomatic knee is bent to approximately 60° (less if painful) Hold for 5 seconds and then slowly slide back up keeping the trunk and buttocks in contact with the wall at all times.	Increase depth of squat.	3 sets of 10. 30 second break period in between sets.
4. Hamstring strengthening seated knee extensions Place a looped thera band/elastic resistance band around the leg of a heavy table or chair. Seated in a chair, place the symptomatic leg in the looped thera band/elastic resistance band with the knee slightly bent. Slowly pull the leg backwards into the elastic band until the knee is bent and a strong resistance is felt. Hold for 5 seconds.	Increase elastic band resistance	3 sets of 10. 30 second break period in between sets.
5. Steps a. Step ups: Place symptomatic leg onto the step.	First increase the height of the step and second add weight.	3 sets of 10. 30-60 second break period in between sets.

Exercise Description	Progression	Repetitions
Slowly step up onto the step. Touch foot of non-affected leg onto the step then place both feet back onto the starting position on the ground.	Weight can be held across the chest with both hands or use two hand weights.	
b. Step downs: Start with both legs standing on top of the step. Bend the knee of the affected leg slowly to lower the non-affected leg towards the ground. Then straighten the affected knee slowly to return to the starting position. The knee of the affected leg must point forward during the movement.	First increase the height of the step and second add weight. Weight can be held across the chest with both hands or use two hand weights.	3 sets of 10. 30-60 second break period in between sets.