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## 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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2022-062577
Article Type:	Protocol
Date Submitted by the Author:	04-Mar-2022
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Keywords:	Knee < ORTHOPAEDIC & TRAUMA SURGERY, REHABILITATION MEDICINE, Clinical trials < THERAPEUTICS

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**TITLE**

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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17 **Word count:** 4198  
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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 effect sizes 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-, therapist- 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 mins of either active or sham rTMS immediately prior to 30 minutes of supervised muscle strengthening exercise (2x/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- 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.

**Registration:** ACTRN12621001712897p

**Keywords:** exercise, knee osteoarthritis, repetitive transcranial magnetic stimulation, clinical trial.

## ARTICLE SUMMARY

### Strengths and limitations

- Randomised, assessor-, therapist- and participant-blind, sham-controlled study design
- Provide data on the feasibility, safety, analgesic effect and central mechanisms of combined rTMS and exercise therapy in knee osteoarthritis
- If trends of efficacy are observed, data will provide support for a fully powered trial
- 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.<sup>1</sup> It is estimated that 10% of people aged over 60 years experience knee osteoarthritis symptoms,<sup>2</sup> resulting in pain and impaired physical function.<sup>3 4</sup> Exercise is the cornerstone of conservative treatment for knee osteoarthritis and recommended by all international guidelines<sup>5</sup>. Although comparable to pharmacological treatments, the effects of exercise are at best, moderate, for pain and function, and small for quality of life.<sup>5</sup> 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.<sup>6-8</sup> This discrepancy has been attributed to maladaptive changes of physiological mechanisms involved in central pain processing.<sup>9</sup> 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),<sup>10</sup> manifesting as pain hypersensitivity.<sup>11</sup> Further, 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.<sup>12 13</sup> For example, M1 organisational changes are associated with poor performance on knee movement tasks<sup>14</sup> and more severe pain is linked to reduced M1 intracortical excitability<sup>15</sup> in people with knee osteoarthritis. Additionally, quadriceps muscle weakness, a hallmark of knee osteoarthritis associated with pain and disability,<sup>16</sup> is associated with voluntary activation deficit, defined as a reduction in neural drive from the central nervous system to the muscles.<sup>17</sup> Reduced M1 excitability and voluntary activation deficit from M1, implicated in quadriceps muscle weakness,<sup>18</sup> may therefore contribute to pain and physical impairments in knee osteoarthritis. Thus, novel treatments

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3 simultaneously targeting these peripheral and central mechanisms could have a beneficial  
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5 impact on pain and function in knee osteoarthritis.  
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10 Repetitive transcranial magnetic stimulation (rTMS), a safe, painless, non-invasive brain  
11 stimulation technique, has been used to alleviate chronic pain by inducing neuroplastic changes  
12 within M1. Neuroimaging evidence suggests that rTMS applied over M1 reduces pain by  
13 activating endogenous opioid systems of brain regions involved in pain processing.<sup>19 20</sup> rTMS  
14 modulates activity in both cortical and subcortical regions, either decreasing (inhibitory, low-  
15 frequency stimulation <1 Hz) or increasing (excitatory, high-frequency stimulation >5 Hz)  
16 cortical excitability.<sup>21</sup> High-frequency rTMS applied over M1 has been shown to produce  
17 superior analgesic effects to low-frequency rTMS in chronic pain populations.<sup>22</sup> Recent meta-  
18 analyses confirmed analgesic effects favouring high-frequency rTMS for short-term relief in  
19 chronic pain.<sup>23</sup> Although a case study reported positive effects on pain and function,<sup>24</sup> clinical  
20 trials of rTMS in knee osteoarthritis are absent.  
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38 Exercise is known to exert peripheral and central effects on pain. Peripherally, exercise  
39 improves muscle strength and coordination and proprioception to enhance control of the joint,  
40 therefore reducing nociceptive input from the affected knee.<sup>25</sup> Centrally, exercise activates  
41 opioidergic pathways and endogenous pain control.<sup>26</sup> Synergistic intervention simultaneously  
42 modulating peripheral (exercise), and central (rTMS and exercise) mechanisms of knee  
43 osteoarthritis could produce greater improvements in pain.<sup>27</sup> Thus, combining high-frequency  
44 rTMS over M1 and exercise has the potential to improve outcomes in knee osteoarthritis  
45 beyond what can be achieved with rTMS or exercise alone. Although pooled data from a recent  
46 meta-analysis in chronic pain showed a moderate reduction in pain severity favouring the  
47 combined rTMS and exercise intervention,<sup>28</sup> no study has investigated this intervention in knee  
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3 osteoarthritis. A proof-of-concept study is needed to determine the feasibility, safety and  
4 participant-rated response to intervention and the effects of such an intervention on pain and  
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6 central mechanisms.  
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12 The aims of this study are to 1) assess the feasibility, safety and perceived patient response to  
13 an intervention adding M1 rTMS to exercise in knee osteoarthritis; 2) elucidate physiological  
14 mechanisms in response to the intervention; and 3) provide data to conduct a sample size  
15 calculation for a fully powered trial.  
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## 23 **METHODS AND ANALYSIS**

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26 This protocol was prepared according to the SPIRIT (Standard Protocol Items for Randomized  
27 Trials) statement (Supplementary Table S1).<sup>29</sup> The trial will be reported following the  
28 CONSORT statement for non-pharmacological treatment (CONSORT-NPT)<sup>30</sup>, the template  
29 for intervention description and replication (TIDieR) checklist and guide<sup>31</sup> and consensus on  
30 exercise reporting template (CERT).<sup>32</sup> It has been prospectively registered with the Australian  
31 and New Zealand Clinical Trials Registry (ACTRN12621001712897p) (Supplementary Table  
32 S2).  
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### 45 **Trial Design**

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47 We will conduct a pilot two-arm parallel-group design, assessor-, therapist- and participant-  
48 blind randomised controlled trial. The outcome measures will be assessed at baseline and  
49 upon treatment completion (six weeks post-randomisation). In addition, measures of pain and  
50 function will also be collected three months post-intervention (Figure 1).  
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### 58 **Participants**

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

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37 Participants in the community in Sydney, Australia will be recruited from local arthritis support  
38 groups, social media platforms and health care providers (medical practitioners,  
39 rheumatologists, orthopaedic surgeons and physiotherapists). Potential participants will first  
40 complete an eligibility screening questionnaire. Those who meet the eligibility criteria will be  
41 contacted by one of the researchers to confirm their willingness to participate in the study and  
42 to arrange the baseline assessment of outcomes. Participants will provide written informed  
43 consent to the outcome assessor on arrival for the baseline assessment.  
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### 56 **Randomisation allocation concealment and blinding**

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3 Participants will be randomly allocated to either: 1) active rTMS + exercise, or 2) sham rTMS  
4 + exercise, based on a 1:1 allocation ratio. The randomisation schedule will be generated by  
5  
6 computer and a researcher not involved in recruitment, treatment provision or assessment. The  
7  
8 randomisation schedule will be concealed in consecutively numbered, sealed opaque envelopes  
9  
10 and given to the researcher who delivers rTMS intervention. Participants will be blinded to the  
11  
12 type of rTMS they will receive and the study hypotheses. All participants will be given the  
13  
14 same instructions and information about the rTMS intervention. Researchers conducting  
15  
16 laboratory-based outcome assessment and physiotherapists providing exercise intervention  
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18 will be blinded to group allocation. Unblinding will be allowed when an adverse or unexpected  
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20 event occurs.  
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### 29 **Outcome Measurements**

30 Measures of feasibility and safety

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32 Feasibility and safety of the rTMS and exercise intervention will be assessed using the  
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34 following measures: (1) the number of sessions attended by each participant (attendance rate >  
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36 80% is considered feasible);<sup>36</sup> (2) the number of drop-outs in each group (drop-out rate < 20%  
37  
38 is considered feasible);<sup>36</sup> (3) the proportion of participants recruited from the total number  
39  
40 screened; (4) willingness of each participant to undergo therapy at baseline on an 11-point NRS  
41  
42 with 'not at all willing' at 0 and 'very willing' at 10 (80% of participants score 7 or more are  
43  
44 considered feasible); (5) success of participant/outcome assessor/therapist blinding; (6) the  
45  
46 number of adverse events and the details of each event.<sup>27</sup> Each adverse event will be considered  
47  
48 separately. One or more serious adverse events will be considered unsafe. The success of  
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50 participant blinding will be assessed at the completion of the intervention using a Yes/No  
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52 response to the question 'Do you believe you received real brain stimulation?' and an 11-point  
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54 NRS of the individual's confidence in that judgement. Participants will also be asked 'Why do  
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3 you believe you received the real/sham brain stimulation?’ and ‘Was it divulged to you whether  
4 you were receiving real brain stimulation or not?’<sup>27</sup> Participant blinding will be considered  
5 successful if there is no difference between active rTMS + exercise and sham rTMS + exercise  
6 groups in the number of participants correctly guessing their treatment allocation at the  
7 completion of the follow-up laboratory assessment.<sup>37</sup> The success of blinding of the outcome  
8 assessor and treating physiotherapists will be determined at the completion of the follow-up  
9 assessment using a Yes/No response to the question ‘Did you know which intervention group  
10 the participant was assigned to before completion of the follow-up laboratory assessment?’ and  
11 ‘If you answer “yes”, how was it divulged to you?’<sup>27</sup> Blinding of the outcome assessor and  
12 treating physiotherapists will be considered successful if they answer “no” to the first question.  
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### 29 Measures of pain and function

30 Knee pain and function will be assessed using: (1) an 11-point NRS for pain when walking in  
31 the past week;<sup>38</sup> (2) the Western Ontario and McMaster Universities (WOMAC) Osteoarthritis  
32 Index (24 items, total score = 96) (Likert version 3.1) and its pain subscale (7 items, total score  
33 = 28) and physical function subscale (17 items, total score = 68), a valid, reliable and  
34 responsive instrument for knee osteoarthritis;<sup>39</sup> (3) the Global Perceived Effect Scale, where  
35 each participant will rate their perceived response to treatments on a 7-point Likert scale  
36 ranging from “completely recovered” to “vastly worsened”;<sup>40</sup> (4) modified painDETECT  
37 (mPD-Q, 7 items, total score = 38), a simple, reliable and valid screening tool to detect a  
38 neuropathic pain component in patients with knee osteoarthritis;<sup>41 42</sup> (5) the number of painful  
39 sites, measured by participants indicating the number of painful sites outside of the affected  
40 knee lasting >24 hours in the past week on a four-sided body map (total score = 35) with higher  
41 scores indicating more widespread hyperalgesia;<sup>43</sup> and (6) the Pain Catastrophising Scale (PCS)  
42 (13 items, total score = 52), a reliable and valid, 13-item self-report instrument to assess  
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3 patients' thoughts and feelings about pain in the domains of magnification, rumination and  
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5 helplessness.<sup>44</sup>  
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10 To assess the long-term effects of the intervention, pain and function will also be assessed three  
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12 months after the completion of intervention via an electronic version of these questionnaires.  
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### 16 17 Measures of physiological mechanisms

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

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21 (1) M1 organisation and function will be measured using an established TMS mapping  
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23 procedure<sup>45</sup>. Participants will be seated in a comfortable chair. Electromyography (EMG) of  
24  
25 the quadriceps muscles will be recorded using bipolar surface electrodes (Ag-AgCl, Noraxon  
26  
27 dual electrodes). The active electrode will be placed over the belly of the rectus femoris (RF),  
28  
29 vastus lateralis (VL) and vastus medialis oblique (VMO) muscles and the ground electrode  
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31 placed at the tibial shaft. EMG signals will be amplified (x2000) and filtered (20 to 1000 Hz),  
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33 and digitally sampled at 2000 Hz using a Power 1902 Data Acquisition System and Spike2  
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35 software (CED Limited, Cambridge, UK).  
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42 Single-pulse TMS delivered over M1 induces a magnetic field over the participant's scalp that  
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44 evokes an electrical current in the underlying M1 tissue resulting in muscle activation recorded  
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46 as motor evoked potentials (MEPs) using EMG. The scalp site evoking the largest MEP  
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48 (termed the "hotspot", the coil position inducing a maximal peak-to-peak MEP amplitude) for  
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50 the RF muscle at a given TMS intensity will be identified.<sup>46</sup> The TMS motor threshold  
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52 assessment tool will be used to determine the active motor threshold (aMT),<sup>47</sup> defined as the  
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54 minimum intensity required to evoke a reliable MEP while participants maintained a muscle  
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3 contraction of 10% averaged root mean square (RMS) EMG of three, 3-s maximal muscle  
4 contractions of the RF muscle.  
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10 During TMS mapping, 126 single-pulse biphasic stimuli (2-s interstimulus interval) will be  
11 delivered pseudorandomly to the scalp over a 6 x 7 cm (7 rows and 8 columns) grid oriented  
12 to the hotspot at 120% aMT of the RF muscle (Magstim Rapid<sup>2</sup>/70mm figure-of-eight coil;  
13 Magstim Ltd., UK). Participants will be asked to activate the RF muscle to 10% of their EMG  
14 recorded during a maximum voluntary contraction (determined as 10% of the highest RMS  
15 EMG for 1 s during three, 3-s maximal muscle contractions performed against manual  
16 resistance in sitting) with feedback provided on a monitor. The coil will be placed tangentially  
17 to the skull with the handle pointing laterally 90 degrees to induce a current in the lateral-to-  
18 medial direction. The Neural Navigator (Neurosoft, Russia) will be used to track the positions  
19 of the TMS coil and participant's head. To minimise muscle fatigue, stimuli will be delivered  
20 in trains of seven stimuli. The neuronavigational display is monitored to ensure adequate  
21 coverage of the grid and that adjacent positions not stimulated consecutively.  
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40 Maps for each of the RF, VL and VMO muscles will be produced offline using a custom  
41 MATLAB script (MathWorks Inc., USA) according to previously published methods.<sup>48,49</sup> RMS  
42 amplitude of EMG traces of the MEPs will be extracted from a 20 to 50ms window after  
43 stimulation and background RMS EMG (55 to 5ms prior to stimulation) will be subtracted.<sup>12</sup>  
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49 <sup>13</sup> A surface map within a transformed plane encompassing stimulation coordinates and their  
50 corresponding MEP amplitude will be generated. The map will then be divided into 2744  
51 partitions (49 x 56), with each partition assigned an estimated MEP amplitude based on the  
52 nearest acquired MEP values using triangular linear interpolation. Partitions with MEP  
53 amplitudes > 10% of the maximum MEP amplitude will be considered as active.<sup>48</sup> Map volume  
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3 is calculated as the sum of MEP amplitudes of all active partitions to index M1 corticomotor  
4 excitability.  
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10 (2) Voluntary activation of the quadriceps muscles will be measured using a twitch  
11 interpolation technique when participants are seated with the hips and knees in 90 degrees  
12 flexion. A force increment will be recorded using a force transducer when an electrical stimulus  
13 delivered by a constant current stimulator (Digitimer, DS7AH) to the femoral nerve 1-2  
14 seconds into the maximal muscle contraction (superimposed twitch), and again 3-4 seconds  
15 afterward when the muscles are at rest (control twitch). Voluntary activation (%) = [1-  
16 (Superimposed twitch/control twitch)] \* 100.<sup>50</sup>  
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28 (3) Pressure pain thresholds (PPTs) will be measured using a hand-held pressure algometer  
29 (Somedc, Hörby, Sweden, probe size 1cm<sup>2</sup>) to quantify mechanical sensitivity. The probe (size  
30 1 cm<sup>2</sup>) will be applied perpendicular to the skin (rate 40 kPa/s) until the participant first reports  
31 that the sensation of pressure has changed to pain. PPTs will be measured at the side of the  
32 knee joint line of the most painful knee and ipsilateral thumbnail. The average of three  
33 measurements at each site will be used in the analysis. PPT measures have been shown to be  
34 reliable in knee osteoarthritis (ICC = 0.83 (0.72-0.90)).<sup>51</sup>  
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47 (4) Conditioned pain modulation (CPM) is a well-established, reliable and safe measure of pain  
48 processing that is thought to reflect endogenous pain inhibition. CPM is assessed as a change  
49 in the pain perceived in one body site (test stimulation) as a result of pain induced in another  
50 body site (conditioned stimulation). We will use PPT measured at the upper trapezius muscle  
51 contralateral to the painful knee as test stimulation<sup>7</sup> and pain is induced in the ipsilateral hand  
52 by cold pressor test (CPT) as conditioned stimulation. Three PPTs (test stimulation) will be  
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3 measured before CPT (conditioned stimulation). For CPT, participants will immerse the hand  
4 in the cold water (4 °C) for a maximum of two minutes.<sup>52</sup> Participants can remove their hand  
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6 prior to the completion of CPT if the pain becomes unbearable and a pain rating on a NRS (0-  
7  
8 100) will be obtained immediately after participants remove their hand. Three PPT  
9  
10 measurements will then be repeated when pain score reaches 50 out of 100 after CPT. A  
11  
12 reduction in PPT indicates deficient endogenous pain inhibition. CPM paradigm has shown  
13  
14 good intrasession reliability (ICC > 0.75).<sup>53</sup>  
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## 22 **Intervention**

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24 Participants will be randomly allocated to either active rTMS + exercise or sham rTMS +  
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26 exercise intervention groups. For participants with bilateral knee pain, the most painful knee  
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28 or the right knee if both knees are equally painful, will be treated. All participants will receive  
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30 a total of 12 treatment sessions (two sessions per week for six weeks). A systematic review  
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32 recommended 12 supervised exercise sessions are needed to be effective for improving pain  
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34 and disability in knee osteoarthritis.<sup>54</sup> Two qualified, registered physiotherapists with clinical  
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36 experience in treating knee osteoarthritis will provide exercise therapy for all participants. A  
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38 researcher trained in the use of rTMS will deliver active and sham rTMS to all participants  
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40 according to their group allocation and will not be blinded to group allocation. Participants will  
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42 be advised to continue with their usual medication during the study. Medications for their knee  
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44 pain will be recorded at baseline and the follow-up laboratory assessment. Data for the  
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46 frequency of use (in the past six months at baseline and during the six-week intervention at  
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48 follow-up) of pain medications will be collected. For each session, participants will receive  
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50 active or sham rTMS (15 minutes) followed by supervised exercise (30 minutes).  
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58 rTMS  
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3 For active rTMS, high-frequency rTMS will be applied to the motor hotspot of the RF muscle  
4 of the treated knee using a Magstim Super Rapid<sup>2</sup> (Magstim Ltd., UK) and a figure-of-eight  
5 air-cooled coil (70 mm). For each session, 3000 stimuli (10 Hz, 30 trains of 10 seconds, 20-  
6 second intertrain interval) will be delivered at 90% of resting motor threshold (rMT).<sup>55</sup> rMT is  
7 defined as the minimum intensity at which 5 out of 10 stimuli, delivered to the hotspot, evoked  
8 a peak-to-peak MEP of at least 50  $\mu$ V.<sup>46</sup> To account for any between-session change in rMT,  
9 participants' rMT will be assessed at the beginning of each treatment session to determine the  
10 stimulation intensity.<sup>56</sup> For sham rTMS, a sham coil that looks identical to a real coil but  
11 produces only audible clicks and no magnetic pulse will be used to deliver the stimulation  
12 protocol identical to the one used for active rTMS. This is the most used sham rTMS protocol  
13 in controlled trials.<sup>12 57 58</sup>

### 30 Exercise

31 Immediately after the rTMS intervention, participants will receive one-to-one quadriceps  
32 strengthening exercise delivered by their treating physiotherapist. A standardised set of  
33 quadriceps strengthening exercises known to be effective in knee osteoarthritis will be  
34 performed using ankle cuff weights or resistance bands, and exercise intensity will be  
35 progressed by the physiotherapist as appropriate for each participant.<sup>5 25 59</sup> A home exercise  
36 program will also be developed and monitored by the physiotherapists for all participants to  
37 perform four times a week during intervention. Participants will complete an exercise diary  
38 and return to their treating physiotherapist weekly for compliance and adherence to their home  
39 exercise program and for recording any adverse effects of home exercise (i.e., whether pain  
40 was present, whether any exercises were difficult, the reason why exercises were unable to be  
41 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 to 20 participants per intervention group is recommended in pilot studies.<sup>60 61</sup> 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.<sup>27</sup>

Measures of feasibility and safety will be analysed descriptively.<sup>62</sup> Within-group changes will be calculated as follow-up minus baseline (mean and standard deviation [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.<sup>63</sup> Due to the limitations of performing statistical comparisons with a small sample size and low power, statistical comparisons between groups will not be conducted.<sup>64</sup> 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.<sup>64</sup> 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).<sup>65</sup> Power will be set at 80% to detect between-group differences, with an  $\alpha$  of 0.05 and a dropout rate based on that of the pilot trial.

### Patient and public involvement

We engaged a consumer representative from 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

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2  
3 potential barriers to participant recruitment. The feedback from the consumer representative  
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5 has been addressed and used to guide the design of intervention and recruitment strategies.  
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## 10 **ETHICS, DATA SAFETY AND DISSEMINATION**

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12 This trial has been approved by the University of New South Wales Human Research Ethics  
13  
14 Committee (HC210954) who may audit the study conduct during the study or after completion.  
15  
16 Any deviation from protocol will require ethics amendment and be updated to the registry. This  
17  
18 study will be terminated if any serious adverse event occurs. A serious adverse event is defined  
19  
20 as any untoward medical occurrence or effect that results in death, or is life-threatening,  
21  
22 requires hospitalisation, results in significant or persistent disability. There will not be a data  
23  
24 monitoring committee due to the relatively short duration of this pilot study.  
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31 Participants' identifiers (i.e., name, address, date of birth, sex, profession) will be removed  
32  
33 from the data. Identifying information will be replaced with a unique anonymous identification  
34  
35 number based on the recruitment order. Each participant will be assigned an anonymous  
36  
37 identification number. This will be used in all further data recording and thus they will be de-  
38  
39 identified. Paperwork that links anonymous identification number to participants' names will  
40  
41 be stored in a locked room. All de-identified data that cannot be linked to an individual  
42  
43 participant will be stored electronically with password protection. There is no perceived need  
44  
45 to re-identify any electronic data. Only aggregate results will be reported therefore it will not  
46  
47 be possible to identify individual participants in any information reported or published from  
48  
49 this study. The data collected in hardcopy will be retained for 15 years after publication and  
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51 electronic data will be stored for a minimum of seven years.  
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3 Study results will be disseminated via presentations at scientific meetings and publications in  
4 a peer-reviewed journal. Publications and presentations related to this study will be authorised  
5 and reviewed by all study investigators.  
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## 10 11 12 **TRIAL STATUS**

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14 This trial will start recruiting in March 2022 and is expected to be completed by December  
15 2022.  
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## 20 21 22 **AUTHOR'S CONTRIBUTION**

23  
24 WJC, SA, JN and SMS were involved in the conception and design of the study protocol. WJC,  
25 SA, JN, NC, HF and SMS contributed to methodology of the study. WJC drafted the  
26 manuscript. All authors edited, reviewed and approved the final protocol.  
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## 33 34 **FUNDING**

35 This work is supported by Australian & New Zealand Musculoskeletal Clinical Trial Network  
36 (Seed Granting Award). The funding body does not have a role in study design and will not  
37 have a role in study execution, data analyses and interpretation or decision to submitting results.  
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## 44 45 **COMPETING INTERESTS**

46 None  
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3 **FIGURE LEGEND**  
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5 **Figure 1. Study flow chart**  
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For peer review only

## APPENDIX - Supplementary Tables

**Table S1. SPIRIT 2013 Checklist**



STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	Item No	Description	Check/details
<b>Administrative information</b>			
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



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4		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
5				
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7				
8	<b>Introduction</b>			
9				
10	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
11				
12		6b	Explanation for choice of comparators	✓ Page 6
13				
14	Objectives	7	Specific objectives or hypotheses	✓ Page 7
15				
16	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
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23	<b>Methods: Participants, interventions, and outcomes</b>			
24				
25	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
26				
27	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
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31	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	✓ Page 14-15
32				
33		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
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4		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	✓ Page 15
5				
6		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	✓ Page 14
7				
8				
9	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcome is strongly recommended	✓ Page 9-14
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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)	✓ Figure 1
16				
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19	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
20				
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23	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	✓ Page 8
24				

### Methods: Assignment of interventions (for controlled trials)

#### Allocation:

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28	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
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33	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
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37	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	✓ Page 9
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4	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	✓ Page 9
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6		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	✓ Page 9
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9	<b>Methods: Data collection, management, and analysis</b>			
10				
11	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
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17		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
18				
19	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
20				
21	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
22				
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25		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	✓ Page 16
26				
27		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
28				
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32	<b>Methods: Monitoring</b>			
33				
34	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
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	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 on 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
<b>Ethics and dissemination</b>			
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

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4	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
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8		31b	Authorship eligibility guidelines and any intended use of professional writers	✓ Page 18
9				
10		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	✓ Page 17
11				
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14	<b>Appendices</b>			
15	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	✓ Approved by Ethics Committee
16				
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18	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
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\*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](https://creativecommons.org/licenses/by-nc-nd/3.0/)” license.

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

<b>Item</b>	<b>Information</b>
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	<p>Inclusion criteria: 1. People aged <math>\geq 50</math> 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.</p> <p>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</p>
Study type	<p>Interventional</p> <p>Purpose of study: treatment</p> <p>Allocation: 1:1 randomised controlled trial: Intervention assignment: parallel; Masking: participant-/therapist-/assessor-blinded</p>

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)



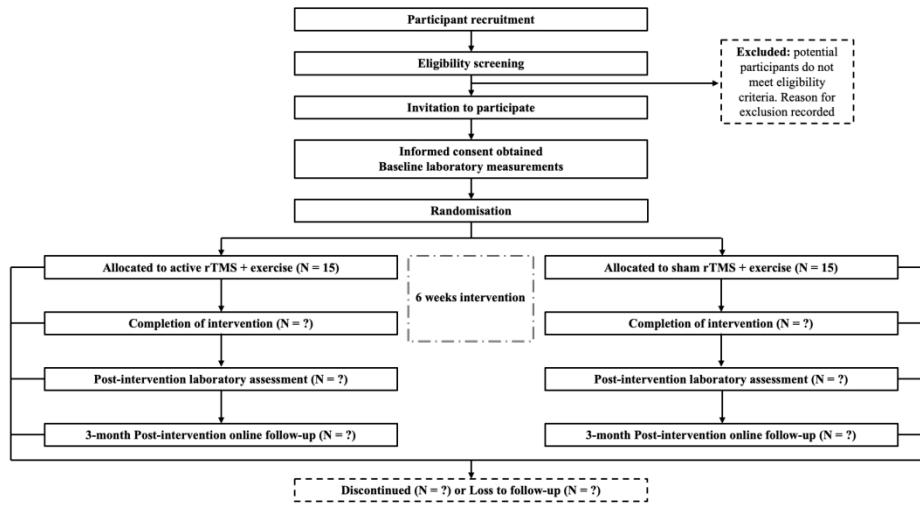


Figure 1. Study flow chart

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# 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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2022-062577.R1
Article Type:	Protocol
Date Submitted by the Author:	05-Jul-2022
Complete List of Authors:	<p>Chang, Wei-Ju; Neuroscience Research Australia, Centre for Pain IMPACT; The University of Newcastle, School of Health Sciences</p> <p>Adie, Sam; UNSW, School of Clinical Medicine, UNSW Medicine &amp; Health; St. George and Sutherland Centre for Clinical Orthopaedic Research (SCORE)</p> <p>Naylor, Justine; Ingham Institute for Applied Medical Research, Whitlam Orthopaedic Research Centre; UNSW, School of Clinical Medicine, UNSW Medicine &amp; Health, South West Clinical Campuses, Discipline of Surgery, Faculty of Medicine and Health</p> <p>Chowdhury, Nahian; Neuroscience Research Australia, Centre for Pain IMPACT</p> <p>Finn, Harrison; Neuroscience Research Australia</p> <p>Rizzo, Rodrigo; Neuroscience Research Australia, Centre for Pain IMPACT; University of New South Wales, School of Medical Sciences</p> <p>O'Hagan, Edel; Neuroscience Research Australia, Centre for Pain IMPACT; University of New South Wales, Prince of Wales Clinical School</p> <p>Schabrun, Siobhan M; Neuroscience Research Australia; Western University, Gray Centre for Mobility and Activity, School of Physical Therapy</p>
<b>Primary Subject Heading</b>:	Rehabilitation medicine
Secondary Subject Heading:	Rheumatology
Keywords:	Knee < ORTHOPAEDIC & TRAUMA SURGERY, REHABILITATION MEDICINE, Clinical trials < THERAPEUTICS

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**TITLE**

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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24 **Word count:** 4192  
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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-, therapist- 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 mins of either active or sham rTMS immediately prior to 30 minutes of supervised muscle strengthening exercise (2x/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- 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.

**Registration:** ACTRN12621001712897p

**Keywords:** exercise, knee osteoarthritis, repetitive transcranial magnetic stimulation, clinical trial.

## ARTICLE SUMMARY

### Strengths and limitations

- Randomised, assessor-, therapist- and participant-blind, sham-controlled study design
- Provide detailed methodology for collecting data on the feasibility, safety, analgesic effect and central mechanisms of combined rTMS 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] Further, 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.

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3 Thus, novel treatments simultaneously targeting these peripheral and central mechanisms could  
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5 have a beneficial impact on pain and function in knee osteoarthritis.  
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10 Repetitive transcranial magnetic stimulation (rTMS), a safe, painless, non-invasive brain  
11 stimulation technique, has been used to alleviate chronic pain by inducing neuroplastic changes  
12 within M1. Neuroimaging evidence suggests that rTMS applied over M1 reduces pain by  
13 activating endogenous opioid systems of brain regions involved in pain processing.[19, 20]  
14 rTMS modulates activity in both cortical and subcortical regions, either decreasing (inhibitory,  
15 low-frequency stimulation <1 Hz) or increasing (excitatory, high-frequency stimulation >5 Hz)  
16 cortical excitability.[21] High-frequency rTMS applied over M1 has been shown to produce  
17 superior analgesic effects to low-frequency rTMS in chronic pain populations.[22] Recent  
18 meta-analyses confirmed analgesic effects favouring high-frequency rTMS for short-term  
19 relief in chronic pain.[23] Although a case study reported positive effects on pain and  
20 function,[24] clinical trials of rTMS in knee osteoarthritis are absent.  
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38 Exercise is known to exert peripheral and central effects on pain. Peripherally, exercise  
39 improves muscle strength and coordination and proprioception to enhance control of the joint,  
40 therefore reducing nociceptive input from the affected knee.[25] Centrally, exercise activates  
41 opioidergic pathways and endogenous pain control.[26] Synergistic intervention  
42 simultaneously modulating peripheral (exercise), and central (rTMS and exercise) mechanisms  
43 of knee osteoarthritis could produce greater improvements in pain.[27] Thus, combining high-  
44 frequency rTMS over M1 and exercise has the potential to improve outcomes in knee  
45 osteoarthritis beyond what can be achieved with rTMS or exercise alone. Although pooled data  
46 from a recent meta-analysis in chronic pain showed a moderate reduction in pain severity  
47 favouring the combined rTMS and exercise intervention,[28] no study has investigated this  
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3 intervention in knee osteoarthritis. A proof-of-concept study is needed to determine the  
4 feasibility, safety and participant-rated response to intervention and the effects of such an  
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6 intervention on pain and central mechanisms.  
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12 The aims of this study are to 1) assess the feasibility, safety and perceived patient response to  
13 an intervention adding M1 rTMS to exercise in knee osteoarthritis; 2) elucidate physiological  
14 mechanisms in response to the intervention; and 3) provide data to conduct a sample size  
15 calculation for a fully powered trial.  
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## 23 **METHODS AND ANALYSIS**

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25 This protocol was prepared according to the SPIRIT (Standard Protocol Items for Randomized  
26 Trials) statement (Supplementary Table S1).[29] The trial will be reported following the  
27 CONSORT statement for non-pharmacological treatment (CONSORT-NPT)[30], the template  
28 for intervention description and replication (TIDieR) checklist and guide[31] and consensus on  
29 exercise reporting template (CERT).[32] It has been prospectively registered with the  
30 Australian and New Zealand Clinical Trials Registry (ACTRN12621001712897p)  
31 (Supplementary Table S2).  
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### 45 **Trial Design**

46 We will conduct a pilot two-arm parallel-group design, assessor-, therapist- and participant-  
47 blind randomised controlled trial. The outcome measures will be assessed at baseline and  
48 upon treatment completion (six weeks post-randomisation). In addition, measures of pain and  
49 function will also be collected three months post-intervention (Figure 1).  
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### 58 **Participants**

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

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37 Participants in the community in Sydney, Australia will be recruited from local arthritis support  
38 groups, social media platforms and health care providers (medical practitioners,  
39 rheumatologists, orthopaedic surgeons and physiotherapists). Potential participants will first  
40 complete an eligibility screening questionnaire. Those who meet the eligibility criteria will be  
41 contacted by one of the researchers to confirm their willingness to participate in the study and  
42 to arrange the baseline assessment of outcomes. Participants will provide written informed  
43 consent to the outcome assessor on arrival for the baseline assessment.  
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### 56 **Randomisation allocation concealment and blinding**

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

30 Measures of feasibility and safety

31 Feasibility and safety of the rTMS and exercise intervention will be assessed using the  
32 following measures: (1) the number of sessions attended by each participant (attendance rate >  
33 80% is considered feasible);[36] (2) the number of drop-outs in each group (drop-out rate <  
34 20% is considered feasible);[36] (3) the proportion of participants recruited from the total  
35 number screened; (4) willingness of each participant to undergo therapy at baseline on an 11-  
36 point NRS with 'not at all willing' at 0 and 'very willing' at 10 (80% of participants score 7 or  
37 more are considered feasible); (5) success of participant/outcome assessor/therapist blinding;  
38 (6) the number of adverse events and the details of each event.[27] Each adverse event will be  
39 considered separately. One or more serious adverse events will be considered unsafe. The  
40 success of participant blinding will be assessed at the completion of the intervention using a  
41 Yes/No response to the question 'Do you believe you received real brain stimulation?' and an  
42 11-point NRS of the individual's confidence in that judgement. Participants will also be asked  
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3 ‘Why do you believe you received the real/sham brain stimulation?’ and ‘Was it divulged to  
4 you whether you were receiving real brain stimulation or not?’[27] Participant blinding will be  
5 considered successful if there is no difference between active rTMS + exercise and sham rTMS  
6 + exercise groups in the number of participants correctly guessing their treatment allocation at  
7 the completion of the follow-up laboratory assessment.[37] The success of blinding of the  
8 outcome assessor and treating physiotherapists will be determined at the completion of the  
9 follow-up assessment using a Yes/No response to the question ‘Did you know which  
10 intervention group the participant was assigned to before completion of the follow-up  
11 laboratory assessment?’ and ‘If you answer “yes”, how was it divulged to you?’[27] Blinding  
12 of the outcome assessor and treating physiotherapists will be considered successful if they  
13 answer “no” to the first question.  
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### 31 Measures of pain and function

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33 Knee pain and function will be assessed using: (1) an 11-point NRS for pain when walking in  
34 the past week;[38] (2) the Western Ontario and McMaster Universities (WOMAC)  
35 Osteoarthritis Index (24 items, total score = 96) (Likert version 3.1) and its pain subscale (7  
36 items, total score = 28) and physical function subscale (17 items, total score = 68), a valid,  
37 reliable and responsive instrument for knee osteoarthritis;[39] (3) the Global Perceived Effect  
38 Scale, where each participant will rate their perceived response to treatments on a 7-point Likert  
39 scale ranging from “completely recovered” to “vastly worsened”;[40] (4) modified  
40 painDETECT (mPD-Q, 7 items, total score = 38), a simple, reliable and valid screening tool to  
41 detect a neuropathic pain component in patients with knee osteoarthritis;[41, 42] (5) the number  
42 of painful sites, measured by participants indicating the number of painful sites outside of the  
43 affected knee lasting >24 hours in the past week on a four-sided body map (total score = 35)  
44 with higher scores indicating more widespread hyperalgesia;[43] and (6) the Pain  
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3 Catastrophising Scale (PCS) (13 items, total score = 52), a reliable and valid, 13-item self-  
4 report instrument to assess patients' thoughts and feelings about pain in the domains of  
5 magnification, rumination and helplessness.[44]  
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12 To assess the long-term effects of the intervention, pain and function will also be assessed three  
13 months after the completion of intervention via an electronic version of these questionnaires.  
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### 17 18 19 Measures of physiological mechanisms

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

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23 (1) M1 organisation and function will be measured using an established TMS mapping  
24 procedure[45]. Participants will be seated in a comfortable chair. Electromyography (EMG) of  
25 the quadriceps muscles will be recorded using bipolar surface electrodes (Ag-AgCl, Noraxon  
26 dual electrodes). The active electrode will be placed over the belly of the rectus femoris (RF),  
27 vastus lateralis (VL) and vastus medialis oblique (VMO) muscles and the ground electrode  
28 placed at the tibial shaft. EMG signals will be amplified (x2000) and filtered (20 to 1000 Hz),  
29 and digitally sampled at 2000 Hz using a Power 1902 Data Acquisition System and Spike2  
30 software (CED Limited, Cambridge, UK).  
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45 Single-pulse TMS delivered over M1 induces a magnetic field over the participant's scalp that  
46 evokes an electrical current in the underlying M1 tissue resulting in muscle activation recorded  
47 as motor evoked potentials (MEPs) using EMG. The scalp site evoking the largest MEP  
48 (termed the "hotspot", the coil position inducing a maximal peak-to-peak MEP amplitude) for  
49 the RF muscle at a given TMS intensity will be identified.[46] The TMS motor threshold  
50 assessment tool will be used to determine the active motor threshold (aMT),[47] defined as the  
51 minimum intensity required to evoke a reliable MEP while participants maintained a muscle  
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3 contraction of 10% averaged root mean square (RMS) EMG of three, 3-s maximal muscle  
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5 contractions of the RF muscle.  
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10 During TMS mapping, 126 single-pulse biphasic stimuli (2-s interstimulus interval) will be  
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12 delivered pseudorandomly to the scalp over a 6 x 7 cm (7 rows and 8 columns) grid oriented  
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14 to the hotspot at 120% aMT of the RF muscle (Magstim Rapid<sup>2</sup>/70mm figure-of-eight coil;  
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16 Magstim Ltd., UK). Participants will be asked to activate the RF muscle to 10% of their EMG  
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18 recorded during a maximum voluntary contraction (determined as 10% of the highest RMS  
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20 EMG for 1 s during three, 3-s maximal muscle contractions performed against manual  
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22 resistance in sitting) with feedback provided on a monitor. The coil will be placed tangentially  
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24 to the skull with the handle pointing laterally 90 degrees to induce a current in the lateral-to-  
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26 medial direction. The Neural Navigator (Neurosoft, Russia) will be used to track the positions  
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28 of the TMS coil and participant's head. To minimise muscle fatigue, stimuli will be delivered  
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30 in trains of seven stimuli. The neuronavigational display is monitored to ensure adequate  
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32 coverage of the grid and that adjacent positions not stimulated consecutively.  
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40 Maps for each of the RF, VL and VMO muscles will be produced offline using a custom  
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42 MATLAB script (MathWorks Inc., USA) according to previously published methods.[48, 49]  
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44 RMS amplitude of EMG traces of the MEPs will be extracted from a 20 to 50ms window after  
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46 stimulation and background RMS EMG (55 to 5ms prior to stimulation) will be subtracted.[12,  
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48 13] A surface map within a transformed plane encompassing stimulation coordinates and their  
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50 corresponding MEP amplitude will be generated. The map will then be divided into 2744  
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52 partitions (49 x 56), with each partition assigned an estimated MEP amplitude based on the  
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54 nearest acquired MEP values using triangular linear interpolation. Partitions with MEP  
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56 amplitudes > 10% of the maximum MEP amplitude will be considered as active.[48] Map  
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3 volume is calculated as the sum of MEP amplitudes of all active partitions to index M1  
4 corticomotor excitability.  
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10 (2) Voluntary activation of the quadriceps muscles will be measured using a twitch  
11 interpolation technique when participants are seated with the hips and knees in 90 degrees  
12 flexion. A force increment will be recorded using a force transducer when an electrical stimulus  
13 delivered by a constant current stimulator (Digitimer, DS7AH) to the femoral nerve 1-2  
14 seconds into the maximal muscle contraction (superimposed twitch), and again 3-4 seconds  
15 afterward when the muscles are at rest (control twitch). Voluntary activation (%) = [1-  
16 (Superimposed twitch/control twitch)] \* 100.[50]  
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28 (3) Pressure pain thresholds (PPTs) will be measured using a hand-held pressure algometer  
29 (Somedc, Hörby, Sweden, probe size 1cm<sup>2</sup>) to quantify mechanical sensitivity. The probe (size  
30 1 cm<sup>2</sup>) will be applied perpendicular to the skin (rate 40 kPa/s) until the participant first reports  
31 that the sensation of pressure has changed to pain. PPTs will be measured at the side of the  
32 knee joint line of the most painful knee and ipsilateral thumbnail. The average of three  
33 measurements at each site will be used in the analysis. PPT measures have been shown to be  
34 reliable in knee osteoarthritis (ICC = 0.83 (0.72-0.90)).[51]  
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47 (4) Conditioned pain modulation (CPM) is a well-established, reliable and safe measure of pain  
48 processing that is thought to reflect endogenous pain inhibition. CPM is assessed as a change  
49 in the pain perceived in one body site (test stimulation) as a result of pain induced in another  
50 body site (conditioned stimulation). We will use PPT measured at the upper trapezius muscle  
51 contralateral to the painful knee as test stimulation[7] and pain is induced in the ipsilateral hand  
52 by cold pressor test (CPT) as conditioned stimulation. Three PPTs (test stimulation) will be  
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3 measured before CPT (conditioned stimulation). For CPT, participants will immerse the hand  
4 in the cold water (4 °C) for a maximum of two minutes.[52] Participants can remove their hand  
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6 prior to the completion of CPT if the pain becomes unbearable and a pain rating on a NRS (0-  
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8 100) will be obtained immediately after participants remove their hand. Three PPT  
9  
10 measurements will then be repeated when pain score reaches 50 out of 100 after CPT. A  
11  
12 reduction in PPT indicates deficient endogenous pain inhibition. CPM paradigm has shown  
13  
14 good intrasession reliability (ICC > 0.75).[53]  
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## 22 **Intervention**

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24 Participants will be randomly allocated to either active rTMS + exercise or sham rTMS +  
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26 exercise intervention groups. For participants with bilateral knee pain, the most painful knee  
27  
28 or the right knee if both knees are equally painful, will be treated. All participants will receive  
29  
30 a total of 12 treatment sessions (two sessions per week for six weeks). A systematic review  
31  
32 recommended 12 supervised exercise sessions are needed to be effective for improving pain  
33  
34 and disability in knee osteoarthritis.[54] Two qualified, registered physiotherapists with  
35  
36 clinical experience in treating knee osteoarthritis will provide exercise therapy for all  
37  
38 participants. A researcher trained in the use of rTMS will deliver active and sham rTMS to all  
39  
40 participants according to their group allocation and will not be blinded to group allocation.  
41  
42 Participants will be advised to continue with their usual medication during the study.  
43  
44 Medications for their knee pain will be recorded at baseline and the follow-up laboratory  
45  
46 assessment. Data for the frequency of use (in the past six months at baseline and during the  
47  
48 six-week intervention at follow-up) of pain medications will be collected. For each session,  
49  
50 participants will receive active or sham rTMS (15 minutes) followed by supervised exercise  
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52 (30 minutes).  
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## rTMS

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<sup>2</sup> (Magstim Ltd., UK) and a figure-of-eight air-cooled coil (70 mm). For each session, 3000 stimuli (10 Hz, 30 trains of 10 seconds, 20-second 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  $\mu$ V.[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 (Supplementary Table S3).[5, 25, 59] A home exercise program will also be developed and monitored by the physiotherapists for all participants to perform four 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 program and for recording any adverse effects of home exercise (i.e., 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 to 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 standard deviation [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  $\alpha$  of 0.05 and a dropout rate based on that of the pilot trial.

## Patient and public involvement

We engaged a consumer representative from the Musculoskeletal Health Clinical Academic Group Consumer Community Council, Australian & New Zealand Musculoskeletal Clinical

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2  
3 Trial Network and received feedback on the study including the proposed intervention and  
4 potential barriers to participant recruitment. The feedback from the consumer representative  
5 has been addressed and used to guide the design of intervention and recruitment strategies.  
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## 10 11 12 **ETHICS, DATA SAFETY AND DISSEMINATION** 13

14 This trial has been approved by the University of New South Wales Human Research Ethics  
15 Committee (HC210954) who may audit the study conduct during the study or after completion.  
16 Any deviation from protocol will require ethics amendment and be updated to the registry. This  
17 study will be terminated if any serious adverse event occurs. A serious adverse event is defined  
18 as any untoward medical occurrence or effect that results in death, or is life-threatening,  
19 requires hospitalisation, results in significant or persistent disability. There will not be a data  
20 monitoring committee due to the relatively short duration of this pilot study.  
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33 Participants' identifiers (i.e., name, address, date of birth, sex, profession) will be removed  
34 from the data. Identifying information will be replaced with a unique anonymous identification  
35 number based on the recruitment order. Each participant will be assigned an anonymous  
36 identification number. This will be used in all further data recording and thus they will be de-  
37 identified. Paperwork that links anonymous identification number to participants' names will  
38 be stored in a locked room. All de-identified data that cannot be linked to an individual  
39 participant will be stored electronically with password protection. There is no perceived need  
40 to re-identify any electronic data. Only aggregate results will be reported therefore it will not  
41 be possible to identify individual participants in any information reported or published from  
42 this study. The data collected in hardcopy will be retained for 15 years after publication and  
43 electronic data will be stored for a minimum of seven years.  
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3 Study results will be disseminated via presentations at scientific meetings and publications in  
4 a peer-reviewed journal. Publications and presentations related to this study will be authorised  
5 and reviewed by all study investigators.  
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## 10 11 12 **TRIAL STATUS**

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14 This trial will start recruiting in March 2022 and is expected to be completed by December  
15 2022.  
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## 19 20 21 **AUTHOR'S CONTRIBUTION**

22  
23 WJC, SA, JMN and SMS were involved in the conception and design of the study protocol.  
24  
25 WJC, SA, JMN, NC, HF, RRNR, EO and SMS contributed to methodology of the study. WJC  
26 drafted the manuscript. All authors edited, reviewed and approved the final protocol.  
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## 31 32 33 **FUNDING**

34  
35 This work is supported by Australian & New Zealand Musculoskeletal Clinical Trial Network  
36 (Seed Granting Award). The funding body does not have a role in study design and will not  
37 have a role in study execution, data analyses and interpretation or decision to submitting results.  
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## 44 45 **COMPETING INTERESTS**

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47 None  
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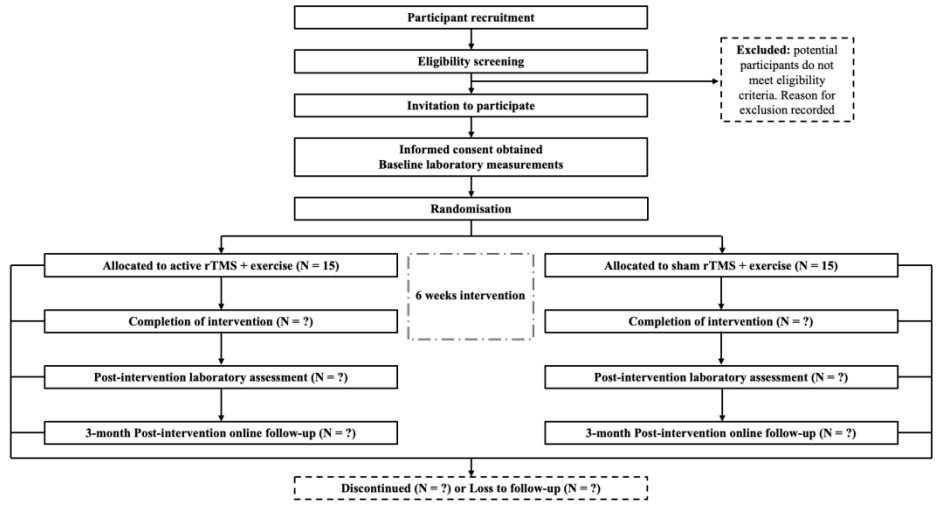
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3 **FIGURE LEGEND**  
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5 **Figure 1. Study flow chart**  
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## APPENDIX - Supplementary Tables

**Table S1. SPIRIT 2013 Checklist**



STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	Item No	Description	Check/details
<b>Administrative information</b>			
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

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4		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
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7				
8	<b>Introduction</b>			
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10	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
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14		6b	Explanation for choice of comparators	✓ Page 6
15	Objectives	7	Specific objectives or hypotheses	✓ Page 7
16				
17	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
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24	<b>Methods: Participants, interventions, and outcomes</b>			
25				
26	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
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29	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
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33	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	✓ Page 14-15
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36		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
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	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

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4	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	✓ Page 9
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6		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	✓ Page 9
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9	<b>Methods: Data collection, management, and analysis</b>			
10				
11	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
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17		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
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21	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
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25	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
26				
27		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	✓ Page 16
28				
29		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
30				
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32	<b>Methods: Monitoring</b>			
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34	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
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	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	✓ 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
<b>Ethics and dissemination</b>			
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

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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
<b>Appendices</b>			
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

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\*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](https://creativecommons.org/licenses/by-nc-nd/3.0/)” license.

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

<b>Item</b>	<b>Information</b>
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	<p>Inclusion criteria: 1. People aged <math>\geq 50</math> 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.</p> <p>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</p>
Study type	<p>Interventional</p> <p>Purpose of study: treatment</p> <p>Allocation: 1:1 randomised controlled trial: Intervention assignment: parallel; Masking: participant-/therapist-/assessor-blinded</p>

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

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

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

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