APPENDIX - Supplementary Tables

Table S1. SPIRIT 2013 Checklist

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

Section/item	Item No	Description	Check/details
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	✓ Page 1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	✓ Page 7
	2b	All items from the World Health Organization Trial Registration Data Set	✓ Table 1
Protocol version	3	Date and version identifier	✓ Table 1
Funding	4	Sources and types of financial, material, and other support	✓ Page 18
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	✓ Page 1, 18
	5b	Name and contact information for the trial sponsor	✓ Table 1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	None

	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Not applicable
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	✓ Page 5-7
	6b	Explanation for choice of comparators	✓ Page 6
Objectives	7	Specific objectives or hypotheses	✓ Page 7
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	✓ Page 7
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	✓ Page 8
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	✓ Page 8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	✓ Page 14-15
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	✓ Page 17

	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	✓ Page 15
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	✓ Page 14
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	✓ Page 9-14
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	✓ Figure 1
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	✓ Page 16
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	✓ Page 8
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	✓ Page 9
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	✓ Page 9
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	✓ Page 9

Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	✓ Page 9
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	✓ Page 9
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	✓ Page 9-14
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	✓ Page 9-14
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	✓ Page 17
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	✓ Page 16
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	✓ Page 16
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	✓ Page 16
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	✓ Page 17

	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	✓ Page 17
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	✓ Page 9
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	✓ Page 17
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	✓ Page 17
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	✓ Page 17
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	✓ Page 8
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Not applicable
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	✓ Page 17
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	✓ Page 18
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	✓ Approved by ethics committee
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	Not applicable

Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	✓ Page 18
	31b	Authorship eligibility guidelines and any intended use of professional writers	✓ Page 18
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	✓ Page 17
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	✓ Approved by Ethics Committee
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Not applicable

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

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

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

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

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

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

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

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

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

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