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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

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ABSTRACT

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

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

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

Trial registration number ACTRN12621001712897p.

STRENGTHS AND LIMITATIONS OF THIS STUDY

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

INTRODUCTION

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

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

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

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

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

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

METHODS AND ANALYSIS

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

Trial design

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

Participants

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

Recruitment

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

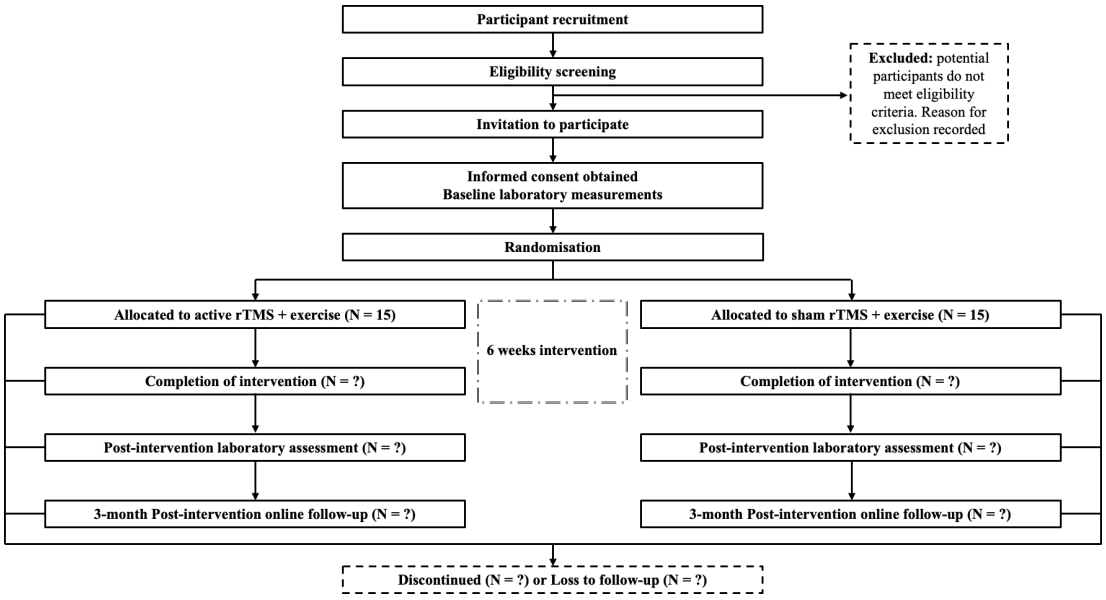

Figure 1 Study flow chart. rTMS, repetitive transcranial magnetic stimulation.

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

Randomisation allocation concealment and blinding

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

Outcome measurements

Measures of feasibility and safety

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

Measures of pain and function

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

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

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

Measures of physiological mechanisms

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

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

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

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

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

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

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

Intervention

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

Repetitive transcranial magnetic stimulation

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

Exercise

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

Sample size and analysis

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

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

Patient and public involvement

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

ETHICS, DATA SAFETY AND DISSEMINATION

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

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

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

Trial status

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

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Competing interests None declared.

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

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