

BMJ Open Effects of combining electrical stimulation of the calf and thigh muscles in patients with osteoarthritis of the knee: protocol for a double-blind, randomised, sham-controlled trial

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ABSTRACT

Introduction Knee osteoarthritis (KOA) is a leading cause of disability and is characterised by degenerative changes causing pain and loss of function. Neuromuscular electrical stimulation (NMES) has been shown to influence muscle size and strength in healthy subjects. A novel self-administered NMES device has been developed to help manage the symptoms of KOA. This study aims to investigate the effects of combining NMES of the calf and quadriceps on individuals with KOA.

Methods and analysis 193 individuals with KOA will be recruited to a single-centre, double-blind, randomised, sham-controlled trial at the Respiratory Biomedical Research Centre, Leicester, UK. Participants will be randomised (1:1) to follow an 8-week home-based intervention using a NMES device or sham device. The NMES device consists of footplate electrodes and two quadriceps electrodes. Footplate stimulation will be completed daily for 30 min and quadriceps stimulation for 20 min, five times a week (compliance is recorded in a self-reported participant diary). The primary outcome is the Western Ontario and McMaster Universities Arthritis Index pain domain, taken at 8 weeks follow-up. Secondary outcomes will explore quadriceps muscle strength, swelling, health-related quality of life, exercise capacity, anxiety and depression, sleep, physical activity and self-reported compliance. A powered subgroup analysis for compliance to the active device will be complete for the primary outcome. Participant focus groups will be completed following recruitment of half of the participants and after all participants have been recruited.

Ethics and dissemination Ethical approval has been obtained from the North-West Preston ethics committee (17/NW/0081). Participants are required to provide informed consent following review of the participant information sheet and discussion regarding study procedures with a member of the research team. The study results will be disseminated to the appropriate stakeholders through presentations, conferences and peer-reviewed journals. Results will be presented to participants following study completion at the Biomedical Research Centre—Respiratory, Glenfield Hospital, Leicester.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This study protocol describes a double-blind, randomised, sham-controlled trial investigating neuromuscular electrical stimulation (NMES) for individuals with osteoarthritis of the knee.
- ⇒ This protocol includes a powered (90%) subgroup analysis for compliance to the active device.
- ⇒ The protocol includes focus groups to understand the participant experience of using NMES for osteoarthritis of the knee.
- ⇒ One limitation of the study is that compliance is measured through self-reported diaries and is not an embedded function of the device.

Trial registration number ISRCTN registry, ISRCTN12112819 (date registered 1 May 2019). IRAS registry 219693. University Hospitals of Leicester registry 91017. Protocol Version 8.

INTRODUCTION

Osteoarthritis (OA) is the most common form of arthritis globally and is one of the leading causes of disability globally.¹ In the UK, 23% of people aged 45 years or older are estimated to have OA with the knee being the most commonly affected joint.² Knee osteoarthritis (KOA) is associated with increased comorbidities and higher mortality rates.^{3,4} OA is also associated with increased healthcare utilisation leading to a significant economic burden.⁵

KOA is driven by a combination of biomechanical and proinflammatory factors causing changes within the joint and periarticular muscles.⁶ Muscular weakness is associated with structural degradation and symptom development in KOA.^{7,8} Exercise is effective for improving pain and physical function in KOA and is recommended in national guidelines.^{9,10} Importantly, strengthening the

periarticular knee muscles is proposed to stabilise the joint, improve shock attenuation and influence underlying inflammatory pathways involved in KOA. Although exercise is recommended, barriers such as pain, self-efficacy and impaired general health status can impact adherence.^{11 12} Other factors such as social isolation and depression are also common in OA populations leading to further challenges in engaging with prescribed exercise programmes.^{13 14} In addition, the pain relieving effect of exercise interventions decreases over time.⁹ Therefore finding an accessible modality that targets both pain and the muscular deficits seen in KOA is desirable.

Neuromuscular electrical stimulation (NMES) provides superficial stimulation to the muscle and generates an alternate activation pattern compared with voluntary contraction.¹⁵ NMES uses low amplitude electrical pulses to stimulate motor neurons and induce muscular contraction. This may be important for pathologies such as KOA where arthrogenic muscle inhibition has been proposed.¹⁶ NMES has been shown to achieve improvements in the knee extensor strength through neural and muscular adaptations.^{17 18} A systematic review found NMES to be effective for improving isometric strength in KOA and to be an appropriate treatment in addition to exercise programmes.¹⁹ NMES achieves consistently high adherence ranging from 81% to 91% for individuals with KOA and is considered a low risk intervention.^{20–22} The post-treatment pain relief experienced while using NMES within the parameters for muscle strengthening may contribute to the high adherence rates.^{20 22}

Due to the current quality of evidence the clinical validity of isolated NMES of the quadriceps for symptomatic KOA remains unclear.²³ Previous trials exploring the effect of NMES for KOA have utilised a wide range of stimulation parameters and training frequencies.¹⁹ In addition, previous research frequently combines NMES with exercise or other modalities; therefore it is difficult to determine the unique impact of NMES from a multifaceted intervention. This has caused significant variability in results with regards to quadriceps strengthening and associated pain relief. Challenges for NMES prescription include individualising the stimulation intensity to individual tolerance while aiming to achieve sufficient stimulation to produce physiological adaptations. Progression of NMES intensity is important during an NMES programme as individuals become habituated to the sensation. Progressing intensity recruits additional muscle fibres at a greater distance from the electrode site increasing the potential area for muscular adaptation.²⁴

NMES investigations frequently include targeting isolated muscle groups in the treatment of KOA.^{20–22 25} Muscle deficits are most frequently reported in the knee extensors compared with the surrounding muscle groups in KOA, although strength deficits are seen throughout the lower limb.²⁶ Compared with healthy controls, individuals with KOA present with weakness and altered activation patterns in the plantarflexors.^{27–29} Both the knee extensors and plantarflexors are important muscle

groups involved in propulsion during the gait cycle. Walking speed is a predictor of function and mortality in older adults and slower walking speed is associated with KOA.³⁰ NMES has been shown to be an effective intervention for increasing strength in the plantarflexors in healthy populations.³¹ To the authors knowledge there have been no previous investigations into calf and foot NMES in the KOA population. It is unknown if stimulating several muscle groups around the knee will provide superior pain relief and functional performance for individuals with KOA.

An NMES device (Revitive Arthritis Knee) has been developed to improve lower limb strength, function, swelling and pain in individuals with KOA. Unlike previous NMES devices, the device provides stimulation to the musculature of the knee both proximally and distally. The device consists of electrodes for quadriceps stimulation and footplate electrodes for stimulation of the calf and foot. The footplate has previously been investigated for its influence on peripheral artery disease and chronic venous disease and was found to significantly improve circulation and walking distance.^{32 33} These investigations did not include quadriceps stimulation and there have been no investigations into the effects of the device for KOA.

The objectives for the trial are: (1) to determine the effects of a NMES device on pain, strength, swelling, health-related quality of life, sleep, anxiety, depression, exercise capacity and physical activity in participants with symptomatic KOA when compared with a sham device; (2) to conduct a subgroup analysis (per protocol) based on compliance, participants who were able to attend the study site prior to and following COVID-19 study site attendance restrictions and recruitment source (eg, orthopaedic clinics, physiotherapy clinics, GP Registers); (3) to conduct focus groups to explore participant experiences of using a NMES device for the management of KOA. The trial hypothesis is an expected 20% difference in the primary outcome (Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain) at 8 weeks between groups in favour of the active device.

METHODS AND ANALYSIS

Trial design and registration

This is a single-centre, double-blind, sham controlled, randomised superiority trial of NMES in KOA. The primary outcome is the WOMAC pain domain.³⁴ The trial is registered on the ISRCTN website (ISRCTN12112819). All trial procedures will be completed at the Centre for Exercise and Rehabilitation Science, NIHR Leicester Biomedical Research Centre—Respiratory, Glenfield Hospital, Groby Road, Leicester, LE3 9QP, UK. Participant visits and the order of outcome measures are described in [figure 1](#).

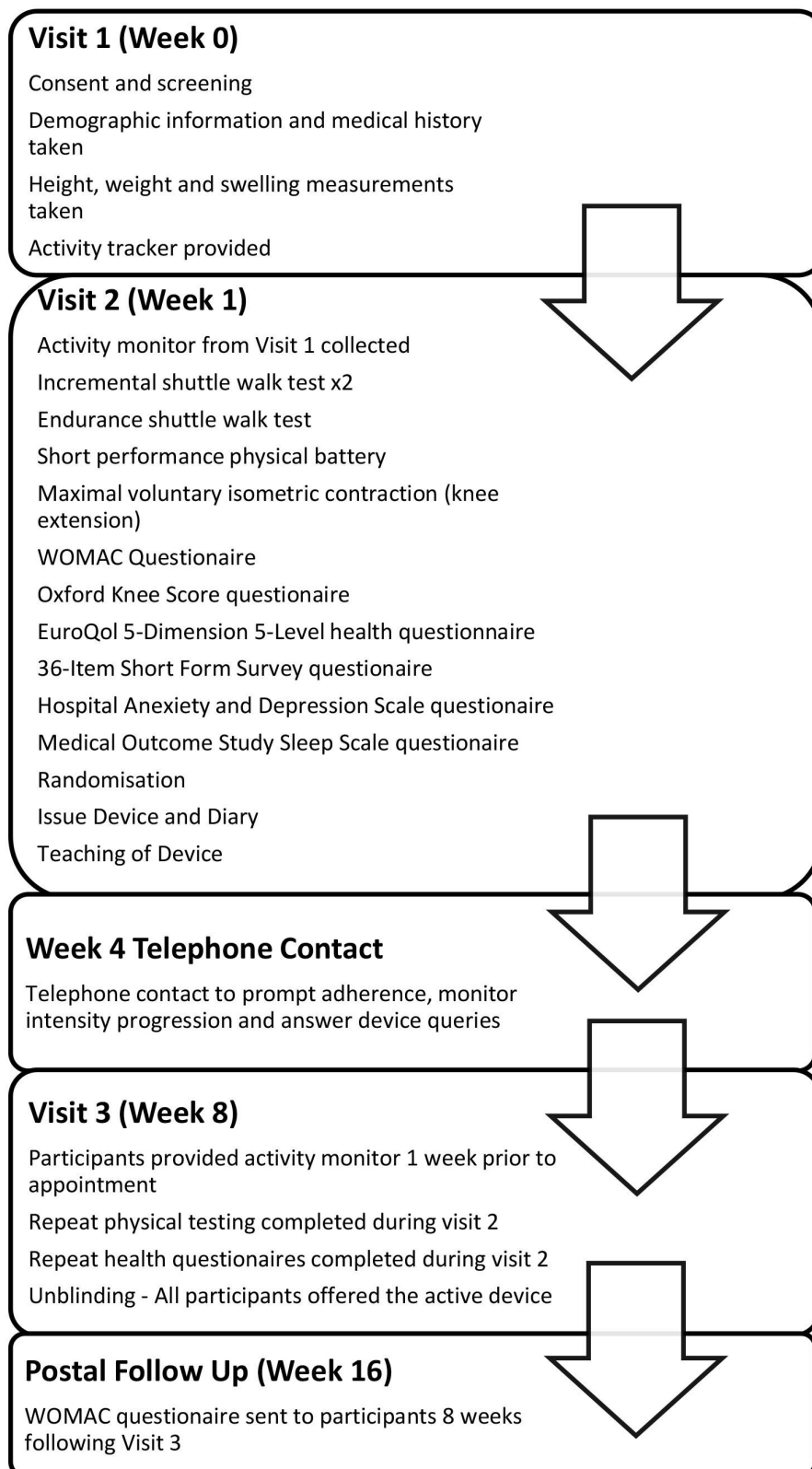


Figure 1 Flow diagram of study procedures. WOMAC, Western Ontario and McMaster Universities Arthritis Index.

Participants

The sample size was calculated to detect a 20% difference (SD=19) between groups using a significance level of 0.05 for the WOMAC pain domain with 90% power. This requires 62 participants to complete the protocol (n=31

in each group). An expected drop-out rate of 30% was predicted, requiring 80 participants in total. In addition, the required recruitment to provide statistical power for the WOMAC pain domain for compliant participants in the active arm was prospectively calculated. Compliance

is defined as completing 20 min of quadriceps stimulation three times per week for each of the 8 weeks. A preplanned analysis of compliance data was performed following the completion of the first 50 participants. An unblinded reviewer (SB-P) observed the active group compliance data only. The compliance level for the active group was 63%. Therefore, a total of 128 participants would be required to be recruited in each arm to allow a powered subgroup analysis for a compliant group within the active arm.

Due to COVID-19 restrictions, 33 participants were unable to attend the study site and complete visit three exercise testing and physical assessments. Therefore, an additional 33 participants will be recruited to account for the altered study engagement in these participants. To account for expected study engagement during the COVID-19 pandemic, the sample size was increased by 20%. In total, 193 participants will be recruited to the trial.

Participants will be recruited from outpatient physiotherapy clinics, orthopaedic outpatient clinics, sports and exercise medicine outpatient clinics and primary care (general practice; GP) registers. Participants will be identified as eligible if they:

- ▶ KOA diagnosed in accordance with National Institute for Health and Care Excellence (NICE) guidelines³⁵

NICE diagnostic criteria: individual is 45 or over, has activity-related joint pain and has either no morning joint-related stiffness or morning stiffness that lasts no longer than 30 min; KOA is diagnosed clinically without requiring radiographic investigations.

- ▶ Aged 45–85 years.

Individuals are excluded from participating in the trial if they are:

- ▶ Fitted with an electronic implant such as a pacemaker or defibrillator
- ▶ Pregnant
- ▶ Existing or undergoing treatment for a deep vein thrombosis (DVT).
- ▶ Significantly impaired cognitive ability
- ▶ Have inflammatory arthritis
- ▶ Have a dermatological condition affecting the feet or legs
- ▶ Have a neurological disorder affecting the feet or legs
- ▶ Have OA of the hip, ankle or foot effecting mobility more than the effected knee.
- ▶ Current or recent knee surgery or injury in the last 3 months.
- ▶ Had a total knee replacement, partial knee replacement or high tibial osteotomy on the knee to be studied
- ▶ Had a corticosteroid or hyaluronic acid injections in the last 6 months.
- ▶ BMI over or equal to 40
- ▶ Completing a concomitant physiotherapy programme.
- ▶ Current use of transcutaneous electrical nerve stimulation.

- ▶ Current or previous use of neuromuscular stimulation device
- ▶ Unable to mobilise
- ▶ Inability to provide informed consent

Randomisation

Participants will complete a consent form at the study site during visit 1 and participants must consent to be randomised to either arm of the study. The study consent form is provided in the online supplemental material. Participants will be randomised at visit 2 using an online randomisation tool (www.sealedenvelope.com). Participants are randomised (1:1) to an active or sham device. Group allocation will be concealed from both the participant and the blinded assessors. Active and sham devices are provided in identical boxes and are closely matched in design. Unblinding is permissible in cases of medical emergencies. All adverse events occurring after randomisation to the study and until the final postal follow-up will be recorded and reported to the study sponsor.

Patient and public involvement

When developing the trial protocol, a patient and public involvement (PPI) meeting was conducted to discuss the feasibility of the intervention and trial visits. Advice from PPI members provided guidance on explaining participant randomisation, administering the device and the format of the participant diaries. Following completion of the trial, participants will be offered the opportunity to attend study steering committee meetings. They will have the opportunity to provide feedback on the trial and guide trial management. Following data analysis, participants will be invited to a dissemination event at the Biomedical Research Centre—Respiratory, Glenfield Hospital, Leicester.

Intervention

The NMES device footplate ([figure 2](#)) provides a 30-min programme of pulsed current with 15 different preprogrammed biphasic waveform patterns. Each pattern lasts approximately 1 min with the 15-min cycle complete twice over the 30-min session. The modulated output with description of frequency, pulse duration, duty cycle (on/off duration) and mid/peak values for voltage and current are described in the online supplemental material. The footplate electrodes require direct contact with the skin and provide bilateral stimulation to the calf and foot. The footplate contains an *IsoRocker* on the base which allows the device to pivot at an angle of 15° permitting plantarflexion of the ankle during stimulation. Participants are instructed to use the 30-min footplate stimulation programme 7 days a week.

The quadriceps stimulation consists of two 10×12.5 cm self-adhesive electrodes for unilateral stimulation ([figure 3](#)). The quadriceps electrodes are placed proximally to rectus femoris motor point and distally covering the vastus medialis motor point.³⁶ The quadriceps electrodes provide two patterns of stimulation allowing users



Figure 2 Neuromuscular electrical stimulation device footplate.

to familiarise with the sensation before entering into a second phase of the strengthening protocol. The quadriceps stimulation programme lasts 20 min and is detailed in the online supplemental material. Participants are instructed to use the 20-min quadriceps stimulation programme five times per week.

Both the footplate and quadriceps stimulation are performed in a seated position. Stimulation is provided in isolation to either the footplate or quadriceps electrodes. Participants are advised to use the footplate and quadriceps stimulation programme in succession during the 5 days each week of completing both programmes. Intensity is displayed on the footplate and ranges from 0 to 99. Intensity is adjusted through the footplate display or remote control. The device contains a stimulation timer which descends once the programme has started. To achieve optimum stimulation intensity, participants are guided by a researcher to achieve a strong muscular contraction during visit 2. They are instructed to progress

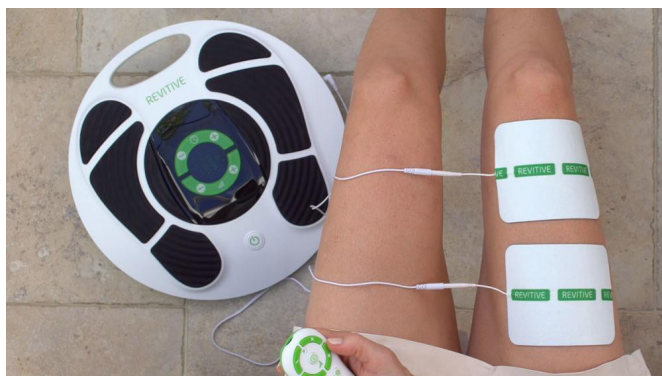


Figure 3 Neuromuscular electrical stimulation quadriceps electrodes.

the intensity on a daily basis as tolerated. Use of the device and peak stimulation intensity achieved each session is recorded in a participant-reported diary provided during visit 2.

The sham device footplate and stimulation pads appear indistinguishable from the active device. The sham device is operationally identical including remote activation and control. The sham device voltage and current is limited to ensure no muscular contraction. When demonstrating the sham device the unblinded researcher will inform the participant that it is expected and normal to not experience a sensation. Participants will have no prior experience of using NMES and will therefore be unable to distinguish between active and sham devices. If a participant is unblinded by information external to the study this will be recorded and they will be asked to continue to complete their 8-week post intervention assessment.

Participants will receive a telephone call from an unblinded member of the research team 4 weeks into the intervention phase. This will provide an opportunity to answer any participant queries, encourage adherence to the intervention and prompt progression of stimulation intensity.

Participants and the visit 3 assessor will remain blinded to the intervention group throughout the trial. After completing visit 3, participants who have received the sham device will be provided with the active device by the unblinded personnel. Following visit 3, participant's continued use of the device is optional and they are not instructed to follow a specific NMES programme.

Outcome measures

All outcomes will be completed prior to administering the intervention and repeated 8 weeks later by a blinded assessor. The WOMAC questionnaire will also be repeated by postal follow-up 8 weeks following visit 3. Apart from the postal follow-up, questionnaires will be completed with an assessor present to support as needed. All measures are described below.

Primary outcome: WOMAC (pain domain)

The WOMAC is a disease-specific questionnaire consisting of 24 questions within three domains: pain, stiffness and function.³⁴ Each domain consists of a 0–4 Likert scale with lower score indicating less severe symptoms or disability. The WOMAC has acceptable reliability and validity in individuals with KOA.³⁷

The primary outcome is the WOMAC pain domain administered prior to the intervention and following the 8-week intervention phase. The WOMAC questionnaire is also sent to participants 16 weeks after randomisation via postal follow-up. The primary end point is 8 weeks following randomisation.

Self-reported knee pain, function and stiffness

Participants will complete the WOMAC and Oxford Knee score.³⁸ The Oxford Knee score comprises of 12 equally weighted questions addressing the patient's perceived

pain and functional ability on a Likert scale with values from 0 to 4, with a reference range of the last 4 weeks. The total score ranges from 0 to 48 and is categorised in the following thresholds: 0–19 severe, 20–29 moderate to severe, 30–39 mild to moderate and 40–48 satisfactory pain.

Health questionnaires

Health status will be measured by the 36-Item Short Form Survey,³⁹ EuroQol 5-Dimension 5-Level health questionnaire,⁴⁰ Medical Outcome Study Sleep Scale⁴¹ and Hospital Anxiety and Depression Score.⁴² Details of each measure are provided in the online supplemental material.

Exercise capacity

Exercise capacity will be measured using the Incremental Shuttle Walk Test (ISWT)⁴³ and Endurance Shuttle Walk Test (ESWT).⁴⁴ Each participant will complete a familiarisation ISWT on visit 2, the ISWT is then repeated following 30 minutes allowing heart rate and blood pressure to return to pre-exercise levels. The ESWT walking speed is calculated based on 80%–85% of the maximum ISWT score. Both the ISWT and ESWT will be completed at visit 2 and visit 3.

Knee extensor strength

The knee extensor strength test is performed seated with 90° hip and knee flexion using an isokinetic dynamometer (Cybex NORM II, CSMi, Stoughton, USA). Knee extensor strength will be measured through 5×10 s maximal voluntary isometric contractions with 60 s rest periods between repetitions. The highest score achieved during strength testing will be used for analysis. Prior to maximal strength testing participants will complete 3×5 s submaximal isometric contractions with 60 s rest periods between repetitions as a warm-up.

Swelling

Swelling of the knee and ankle will be assessed through joint line circumference measurements of the knee and ankle at week 0 and week 8 using a flexible tape measure. Three measurements will be taken and the mean calculated. Measurements will be taken prior to randomisation and repeated by a blinded assessor on visit 3. Circumference measurements of the knee have been shown to achieve high levels of inter-rater reliability.⁴⁵

Physical activity

Participants will wear an ActiGraph GT3X activity monitor (ActiGraph, Pensacola, Florida, USA) during waking hours for 7 days between visit 1 (week 0) and visit 2 (week 1). Participants will also wear the device during waking hours for 7 days prior to visit 3. The ActiGraph GT3X activity monitor cannot be worn during water-based activities. Physical activity data will be analysed using ActiLife software (Actigraph).

Compliance

Compliance for both groups is defined as completing 20 min of quadriceps stimulation three times per week for each of the 8 weeks. Compliance to the intervention for both groups will be recorded in a self-reported participant diary provided at visit 2. The diary will record the date of use, time of use, stimulation location ('thigh pads' or 'footplate'), duration of use and peak intensity level achieved. There will also be a section provided for participants to record any changes in pain medication, activity levels, health status or other healthcare interventions.

Qualitative focus groups

Focus groups will be completed following recruitment of half the trial participants (n=80) and following recruitment of all participants (n=160). A mid-recruitment focus group has been selected to reduce the recall period for participants who were recruited prior to the midpoint. The focus groups will aim to understand the experience of using NMES for the management of KOA. This includes the factors impacting compliance during and after the trial. Each focus group will include approximately eight participants. All participants from both sham and active groups who consent to be contacted will be invited to participate in the focus groups. The sham group will have experience using NMES after being provided the active device following completion of the trial. The focus groups will be conducted in person in a hospital setting or virtually by a member of the research team. A researcher diary will be kept for purposes of reflexivity and to support data analysis and theme development.

Data analysis plan

Data collected will be entered into a secure online database 'Research Electronic Data Capture' (REDCap)^{46 47} by authorised members of the researcher team. Prior to analysis a study data check will be completed by a second study researcher. Baseline characteristics will be described and group comparison will be analysed using an independent t-test or non-parametric test. An intention to treat analysis will be completed. Changes in all outcomes will be described preintervention and postintervention and analysed using paired t-test's or non-parametric equivalent, the primary outcome being the WOMAC pain domain at 8 weeks. Differences between time points and groups will be compared using repeated measures analysis of variance (ANOVA). Baseline scores will be included as covariates within the ANOVA analysis to account for any significant differences. The WOMAC questionnaire will also be compared between groups at the 16-week time point. An analysis of 'responders' and 'non-responders' will be explored for all outcomes following data collection. Responders are defined as participants who achieve a 20% improvement in the primary outcome during the 8-week intervention phase.

Predefined subgroup analyses will be performed on: (1) compliant versus non-compliant (compliance defined within compliance section above), a per-protocol analysis,

(2) participants who were able to attend the study site prior to and following COVID-19 study site attendance restrictions and (3) recruitment source (eg, orthopaedic clinics, physiotherapy clinics, GP Registers). Further exploratory analyses will be performed on physical activity measures.

Qualitative focus groups will be transcribed verbatim and analysed through NVivo V.12 (QSR International) using thematic analysis.⁴⁸ The main themes generated from the analysis will be discussed with participants of the focus groups to ensure the discussion was represented accurately.

ETHICS AND DISSEMINATION

Ethical approval was provided by the North-West Preston Research Ethics Committee on the 22 February 2017 (17/NW/0081). Participants provided informed consent following review of the participant information sheet and discussion regarding study procedures with a member of the research team. Findings from the trial will indicate the clinical effectiveness of this NMES device. Conduct of the trial began on 13 May 2019 and the data collection will be completed within 2022. These findings will be disseminated in line with the Centre for Exercise and Rehabilitation Science dissemination strategy and will be submitted for publication in a peer-reviewed journal.

Dissemination will be completed to participants of the trial and more broadly to healthcare professionals, patients, members of the public and academics. The results of the study will be presented at regional and national musculoskeletal conferences.

Due to the ongoing COVID-19 pandemic, the protocol procedures may be altered as necessary for participant safety. Any adaptations will be discussed in the publication of the study and via ISRCTN.

Composition, roles, and responsibilities

Trial processes and data are managed and audited within the University Hospitals of Leicester. The study sponsor (Actegy Ltd) will have access to anonymised trial data following the completion of all data collection. Trial analysis will be completed by the research team within University Hospitals of Leicester or an independent statistician.

Protocol modifications

Trial registries, research ethics committee, study sponsor and participants will be informed of any protocol modifications by a member of the study team from University Hospitals of Leicester.

Primary trial sponsor

Actegy Ltd (Bracknell, UK).

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Contributors SJS is the principal investigator of the research trial. SJS, SB-P, LH-W, ED, LL and CE were involved in the development of the intervention and design of the trial. SJS, SB-P, LH-W, ED, LL, CE, CG and GEM have been involved in drafting the work or revising it critically for important intellectual content and have given the final approval of the version published.

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Competing interests S Singh reports grants from Actegy Ltd during the conduct of the study.

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

Patient consent for publication Not applicable.

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