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# BMJ Open

## Protocol for a Double Blind, Randomised, Sham-Controlled Trial Investigating the Effects of Combining Electrical Stimulation of the Calf and Thigh Muscles in Patients with Osteoarthritis of the Knee

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Keywords:	Knee < ORTHOPAEDIC & TRAUMA SURGERY, Rehabilitation medicine < INTERNAL MEDICINE, Musculoskeletal disorders < ORTHOPAEDIC & TRAUMA SURGERY

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7 Osteoarthritis of the Knee  
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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 increase muscle strength in the quadriceps, calf and foot and improve function to help manage the symptoms of knee osteoarthritis.

### Methods and Analysis

Individuals with knee osteoarthritis will be recruited to a double blind, randomised, sham-controlled trial. Both groups will follow an 8 week home-based intervention using a NMES device or a sham device. The NMES device consists of footplate electrodes providing stimulation to the calf and foot and two quadriceps stimulation electrodes. Footplate stimulation will be completed daily for 30 minutes and quadriceps stimulation for 20 minutes, 5 times a week (compliance is recorded in a self-reported participant diary). The primary outcome is the Western Ontario and McMaster Universities Arthritis Index (WOMAC) 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 sub group analysis for compliance to the active device will be complete for the primary

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3 outcome. Participant focus groups will be completed following recruitment of half of the  
4  
5 participants and after all participants have been recruited. Focus groups will be analysed via  
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7 thematic analysis.  
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## 10 11 12 13 14 15 **Ethics and Dissemination**

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18 Ethical approval has been obtained from the North-West Preston ethics committee and the  
19  
20 trial has been registered through the ISRCTN registry (ISRCTN12112819). The study results  
21  
22 will be disseminated to the appropriate stakeholders through presentations, conferences  
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24 and peer-reviewed journals. Results will be presented to participants following study  
25  
26 completion at the Biomedical Research Centre – Respiratory, Glenfield Hospital, Leicester.  
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## 34 **ARTICLE SUMMARY** (Strengths and limitations of this study)

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37 • This study protocol describes a double-blind, randomised, sham-controlled trial  
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39 investigating neuromuscular electrical stimulation (NMES) for individuals with  
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41 osteoarthritis of the knee  
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45 • This protocol includes a powered (80%) sub group analysis for compliance to the  
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47 active device  
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51 • The protocol includes focus groups to understand the participant experience of  
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53 using NMES for osteoarthritis of the knee  
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- 56  
57 • Limitation: compliance is measured through self-reported diaries and is not an  
58  
59 embedded function of the device  
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## COVID-19

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.

## INTRODUCTION

Osteoarthritis (OA) is the most common form of arthritis and is one of the leading causes of disability globally [1]. In the United Kingdom, 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

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3 of exercise interventions decreases over time [9]. Therefore finding an accessible modality  
4 that targets both pain and the muscular deficits seen in KOA is desirable.  
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9 Neuromuscular electrical stimulation (NMES) provides superficial stimulation to the muscle  
10 and generates an alternate activation pattern compared to voluntary contraction [15].  
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14 NMES uses low amplitude electrical pulses to stimulate motor neurons and induce muscular  
15 contraction. This may be important for pathologies such as KOA where arthrogenic muscle  
16 inhibition has been proposed [16]. NMES has been shown to achieve improvements in the  
17 knee extensor strength through neural and muscular adaptations [17, 18]. A systematic  
18 review found NMES to be effective for improving isometric strength in KOA and to be an  
19 appropriate treatment in addition to exercise programmes [19]. NMES achieves consistently  
20 high adherence ranging from 81% - 91% for individuals with KOA and is considered a low risk  
21 intervention [20-22]. The post-treatment pain relief experienced while using NMES within  
22 the parameters for muscle strengthening may contribute to the high adherence rates [20,  
23 22].  
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39 Due to the current quality of evidence the clinical validity of NMES for symptomatic KOA  
40 remains unclear [23]. Previous trials exploring the effect of NMES for KOA have utilised a  
41 wide range of stimulation parameters and training frequencies [19]. In addition, previous  
42 research frequently combines NMES with exercise or other modalities; therefore it is  
43 difficult to determine the unique impact of NMES from a multifaceted intervention. This has  
44 caused significant variability in results with regards to quadriceps strengthening and  
45 associated pain relief. Challenges for NMES prescription include individualising the  
46 stimulation intensity to individual tolerance whilst aiming to achieve sufficient stimulation  
47 to produce physiological adaptations. Progression of NMES intensity is important during an  
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3 NMES programme as individuals become habituated to the sensation. Progressing intensity  
4 recruits additional muscle fibres at a greater distance from the electrode site increasing the  
5  
6 potential area for muscular adaptation [24].  
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11 NMES investigations frequently include targeting isolated muscle groups in the treatment of  
12  
13 KOA [20-22, 25]. Muscle deficits are most frequently reported in the knee extensors  
14  
15 compared to the surrounding muscle groups in KOA, although strength deficits are seen  
16  
17 throughout the lower limb [26]. Compared to healthy controls, individuals with KOA present  
18  
19 with weakness and altered activation patterns in the plantarflexors [27-29]. Both the knee  
20  
21 extensors and plantarflexors are important muscle groups involved in propulsion during the  
22  
23 gait cycle. Walking speed is a predictor of function and mortality in older adults and slower  
24  
25 walking speed is associated with KOA [30]. NMES has been shown to be an effective  
26  
27 intervention for increasing strength in the plantarflexors in healthy populations [31]. To the  
28  
29 authors knowledge there have been no previous investigations into calf and foot NMES in  
30  
31 the KOA population. It is unknown if stimulating several muscle groups around the knee will  
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33 provide superior pain relief and functional performance for individuals with KOA.  
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41 An NMES device (Revitive Arthritis Knee®) has been developed to improve lower limb  
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43 strength, function, swelling and pain in individuals with KOA. The device consists of  
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45 electrodes for quadriceps stimulation and footplate electrodes for stimulation of the calf  
46  
47 and foot. The footplate has previously been investigated for its influence on peripheral  
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49 artery disease and chronic venous disease and was found to significantly improve circulation  
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51 and walking distance [32, 33]. These investigations did not include quadriceps stimulation  
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53 and there have been no investigations into the effects of the device for KOA.  
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3 The objectives for the trial are: 1) to determine the effects of a NMES device on pain,  
4 strength, swelling, health related quality of life, sleep, anxiety, depression, exercise capacity  
5 and physical activity in participants with symptomatic KOA when compared with a sham  
6 device; 2) to conduct a subgroup analysis (per protocol) based on compliance, self-  
7 administered stimulation intensity, baseline pain and function and knee extensor strength  
8 to explore if there is a subgroup of patients who receive the most benefit from NMES 3) to  
9 conduct focus groups to explore participant experiences of using a NMES device for the  
10 management of KOA.  
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## 27 **METHODS AND ANALYSIS**

### 28 **Trial Design and Registration**

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33 This is a single centre, double-blind, sham controlled, randomised superiority trial of NMES  
34 in KOA. The primary outcome is the Western Ontario and McMaster Universities  
35 Osteoarthritis Index (WOMAC) pain domain [34]. The trial is registered on the ISRCTN  
36 website (ISRCTN12112819). All trial procedures will be completed at the Centre for Exercise  
37 and Rehabilitation Science, NIHR Leicester Biomedical Research Centre – Respiratory,  
38 Glenfield Hospital, Groby Road, Leicester, LE3 9QP, UK. Participant visits and the order of  
39 outcome measures are described in figure 1.  
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## 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 80% power. This requires 96 participants to complete the protocol (n=48 in each group). 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 minutes of quadriceps stimulation 3 times per week for each of the 8 weeks. A pre-planned analysis of compliance data was performed following the completion of the first 50 participants. An unblinded reviewer (SBP) observed the active group compliance data only. The compliance level for the active group was 63%. Therefore a total of 80 participants will be recruited in each arm to allow a powered subgroup analysis for a compliant group within the active arm.

Participants will be recruited from outpatient physiotherapy clinics, orthopaedic out-patient 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 NICE guidelines [35]
- 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 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 significant OA of the hip, ankle or foot
- 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 (TENS)
- Current or previous use of neuromuscular stimulation device
- Unable to mobilise
- Inability to provide informed consent

## Randomisation

Participants must consent to be randomised to either arm of the study. Participants will be randomised at visit 2 using an online randomisation tool ([www.sealedenvelope.com](http://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 (PPI)

When developing the trial protocol a 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 minute programme of pulsed current with 15 different preprogrammed biphasic waveform patterns. Each pattern lasts approximately 1 minute with the 15 minute cycle complete twice over the 30 minute 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 supplementary 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 degrees permitting plantarflexion of the ankle during stimulation. Participants are instructed to use the 30 minute footplate stimulation programme 7 days a week.

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3 The quadriceps stimulation consists of two 10x12.5cm self-adhesive electrodes for unilateral  
4 stimulation (Figure. 3). The quadriceps electrodes are placed proximally to rectus femoris  
5 motor point and distally covering the vastus medialis motor point [36]. The quadriceps  
6 electrodes provide two patterns of stimulation allowing users to familiarise with the  
7 sensation before entering into a second phase of the strengthening protocol. The  
8 quadriceps stimulation programme lasts 20 minutes and is detailed in the supplementary  
9 material. Participants are instructed to use the 20 minute quadriceps stimulation  
10 programme 5 times per week.  
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23 Both the footplate and quadriceps stimulation is performed in a seated position. Stimulation  
24 is provided in isolation to either the footplate or quadriceps electrodes. Participants are  
25 advised to use the footplate and quadriceps stimulation programme in succession during  
26 the 5 days each week of completing both programmes. Intensity is displayed on the  
27 footplate and ranges from 0 to 99. Intensity is adjusted through the footplate display or  
28 remote control. The device contains a stimulation timer which descends once the  
29 programme has started. To achieve optimum stimulation intensity participants are guided  
30 by a researcher to achieve a strong muscular contraction during visit 2. They are instructed  
31 to progress the intensity on a daily basis as tolerated. Use of the device and peak  
32 stimulation intensity achieved each session is recorded in a participant reported diary  
33 provided during visit 2.  
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51 The sham device footplate and stimulation pads appear indistinguishable from the active  
52 device. The sham device is operationally identical including remote activation and control.  
53 The sham device voltage and current is limited to ensure no muscular contraction. When  
54 demonstrating the sham device the unblinded researcher will inform the participant that it  
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3 is expected and normal to not experience a sensation. Participants will have no prior  
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5 experience of using NMES and will therefore be unable to distinguish between active and  
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7 sham devices.  
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11 Participants will receive a telephone call from an unblinded member of the research team  
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13 four weeks into the intervention phase. This will provide an opportunity to answer any  
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15 participant queries, encourage adherence to the intervention and prompt progression of  
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17 stimulation intensity.  
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21 Participants and the visit 3 assessor will remain blinded to the intervention group  
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23 throughout the trial. After completing visit 3, participants who have received the sham  
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25 device will be provided with the active device by the unblinded personnel. Following visit 3,  
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27 participant's continued use of the device is optional and they are not instructed to follow a  
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29 specific NMES programme.  
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### 38 **Outcome Measures**

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41 All outcomes will be completed prior to administering the intervention and repeated 8  
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43 weeks later by a blinded assessor. The WOMAC questionnaire will also be repeated by  
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45 postal follow up 8 weeks following visit 3. Apart from the postal follow up, questionnaires  
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47 will be completed with an assessor present to support as needed. All measures are  
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49 described below.  
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## **Primary Outcome – Western Ontario and McMaster Universities Arthritis Index (WOMAC)**

### **(Pain Domain)**

The WOMAC is a disease specific questionnaire consisting of 24 questions within 3 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 form 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-severe, 30-39 mild-moderate and 40-48 satisfactory pain.

### **Health Questionnaires**

Health status will be measured by the 36-Item Short Form Survey (SF-36) [39], EuroQol 5-Dimension 5-Level health questionnaire (EQ-5D-5L) [40], Medical Outcome Study Sleep



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3 Scale (MOS Sleep) [41] and Hospital Anxiety and Depression Score (HADS) [42]. Details of  
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5 each measure are provided in the supplementary material.  
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### 11 **Exercise Capacity**

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

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37 The knee extensor strength test is performed seated with 90 degrees hip and knee flexion  
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39 using an isokinetic dynamometer (Cybex NORM II, CSMi, Stoughton, USA). Knee extensor  
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41 strength will be measured through 5 x 10 second maximal voluntary isometric contractions  
42  
43 with 60 second rest periods between repetitions. The highest score achieved during  
44  
45 strength testing will be used for analysis. Prior to maximal strength testing participants will  
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47 complete 3 x 5 second sub maximal isometric contractions with 60 second rest periods  
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52 between repetitions as a warm-up.  
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## 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, FL, 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 minutes of quadriceps stimulation 3 times per week for each of the 8 weeks. Compliance to the intervention 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

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3 intensity level achieved. There will also be a section provided for participants to record any  
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5 changes in pain medication, activity levels, health status or other health care interventions.  
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### 10 11 12 **Qualitative Focus Groups**

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15 Focus groups will be completed following recruitment of half the trial participants and  
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17 following recruitment of all participants. The focus groups will aim to understand the  
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19 experience of using NMES for the management of KOA. This includes the factors impacting  
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21 compliance during and after the trial. Each focus group will include approximately 8  
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23 participants. All participants from both sham and active groups who consent to be  
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25 contacted will be invited to participate in the focus groups. The sham group will have  
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27 experience using NMES after being provided the active device following completion of the  
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29 trial. The focus groups will be conducted in person in a hospital setting or virtually by a  
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31 member of the research team. A researcher diary will be kept for purposes of reflexivity and  
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33 to support data analysis and theme development.  
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### 44 **Data analysis plan**

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47 Data collected will be entered into a secure online database 'Research Electronic Data  
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49 Capture' (REDCap) [46. 47] by authorised members of the researcher team. Baseline  
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51 characteristics will be described and group comparison will be analysed using an  
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53 independent t-test or non-parametric test. An intention to treat analysis will be completed.  
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55 Changes in all outcomes will be described pre and post intervention and analysed using  
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57 paired t-test's or non-parametric equivalent, the primary outcome being the WOMAC pain  
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3 domain at 8 weeks. Differences between time points and groups will be compared using  
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5 repeated measures ANOVA. Baseline scores will be included as covariates within the ANOVA  
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7 analysis to account for any significant differences. The WOMAC questionnaire will also be  
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9 compared between groups at the 16 week time point. An analysis of 'responders' and 'non-  
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11 responders' will be explored for all outcomes following data collection. Responders are  
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13 defined as participants who achieve a 20% improvement in the primary outcome during the  
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15 8-week intervention phase.  
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19 Pre-defined subgroup analyses will be performed on: 1) compliant versus non-compliant  
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21 (compliance defined within compliance section above) a per protocol analysis, 2)  
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23 participants who were able to attend the study site prior to and following COVID-19 study  
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25 site attendance restrictions 3) recruitment source (e.g orthopaedic clinics, physiotherapy  
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27 clinics, GP Registers). Further exploratory analyses will be performed on physical activity  
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29 measures.  
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36 Qualitative focus groups will be transcribed verbatim and analysed through NVivo version  
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38 12 (QSR International) using thematic analysis [48]. The main themes generated from the  
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40 analysis will be discussed with participants of the focus groups to ensure the discussion was  
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42 represented accurately.  
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## 50 **ETHICS AND DISSEMINATION**

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53 Ethical approval was provided by the North-West Preston Research Ethics Committee on the  
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55 22<sup>nd</sup> February 2017. Findings from the trial will indicate the clinical effectiveness of this  
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57 NMES device. The findings of this trial are expected to be published and publically available  
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3 within 2022. These findings will be disseminated in line with the Centre for Exercise and  
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5 Rehabilitation Science dissemination strategy. Dissemination will be completed to  
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7 participants of the trial and more broadly to health care professionals, patients, members of  
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9 the public and academics. The results of the study will be presented at regional and national  
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11 musculoskeletal conferences.  
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### 19 **AUTHORS' CONTRIBUTIONS**

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22 All authors co-developed the protocol. The manuscript was prepared by S.Briggs-Price and  
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24 approved by all authors.  
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### 31 **FUNDING STATEMENT**

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34 This research was supported by an educational grant from Actegy Ltd (Bracknell, UK).  
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### 41 **COMPETING INTERESTS STATEMENT**

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43  
44 S. Singh reports grants from Actegy Ltd during the conduct of the study  
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3 **Figure Legends**  
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7 **Figure.1 Flow diagram of study procedures**  
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12 **Figure.2 NMES Device Footplate**  
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17 **Figure.3 NMES Quadriceps Electrodes**  
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3 **Figure 1. Flow diagram of study procedures**  
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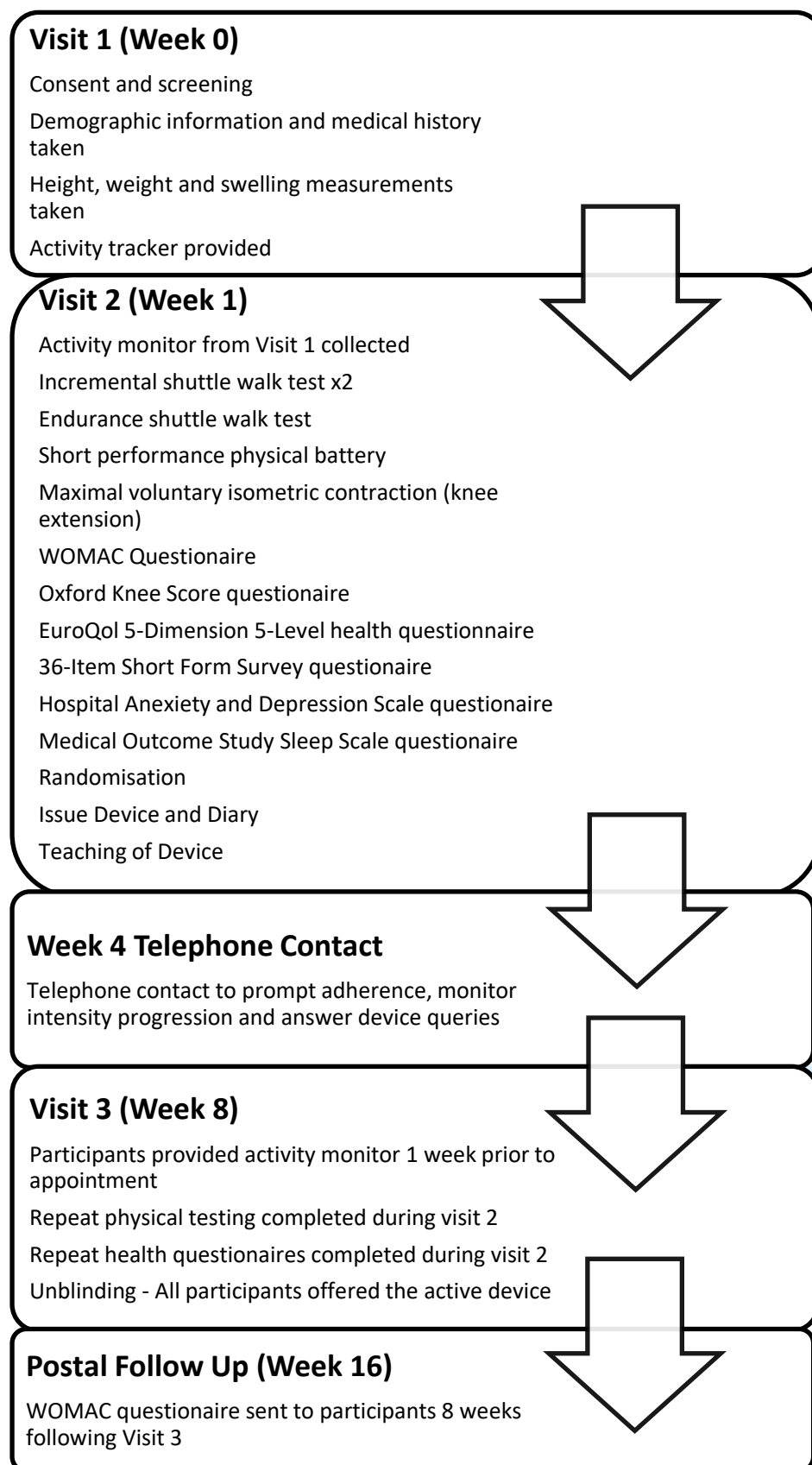




Figure.2 NMES Device Footplate

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Figure.3 NMES Quadriceps Electrodes

264x148mm (96 x 96 DPI)

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# BMJ Open

## Protocol for a Double Blind, Randomised, Sham-Controlled Trial Investigating the Effects of Combining Electrical Stimulation of the Calf and Thigh Muscles in Patients with Osteoarthritis of the Knee

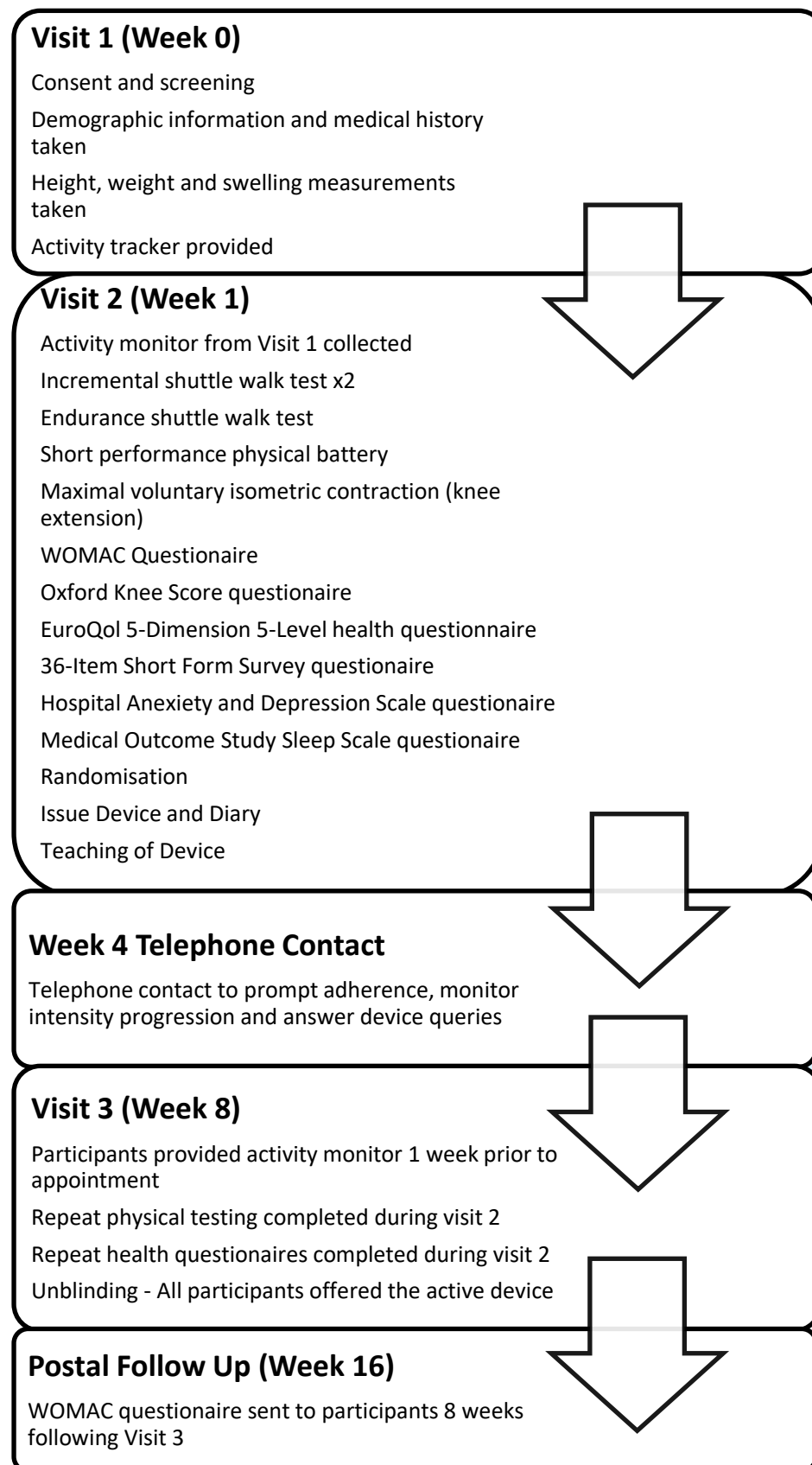
Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2022-061113.R1
Article Type:	Protocol
Date Submitted by the Author:	14-Jun-2022
Complete List of Authors:	Briggs-Price, Samuel; University Hospitals of Leicester NHS Trust, Centre for Exercise and Rehabilitation Sciences, NIHR Leicester Biomedical Research Centre – Respiratory, Glenfield Hospital Houchen-Wolloff, Linzy; University Hospitals of Leicester NHS Trust, Centre for Exercise and Rehabilitation Sciences, NIHR Leicester Biomedical Research Centre – Respiratory, Glenfield Hospital; University of Leicester, Department of Respiratory Sciences Daynes, Enya; University Hospitals of Leicester NHS Trust, Centre for Exercise and Rehabilitation Sciences, NIHR Leicester Biomedical Research Centre – Respiratory, Glenfield Hospital Gerlis, Charlotte; University Hospitals of Leicester NHS Trust, Centre for Exercise and Rehabilitation Sciences, NIHR Leicester Biomedical Research Centre – Respiratory, Glenfield Hospital Latimer, Lorna; University Hospitals of Leicester NHS Trust, Centre for Exercise and Rehabilitation Sciences, NIHR Leicester Biomedical Research Centre – Respiratory, Glenfield Hospital; University of Leicester, Department of Respiratory Sciences Mills, George; University Hospitals of Leicester NHS Trust, Centre for Exercise and Rehabilitation Sciences, NIHR Leicester Biomedical Research Centre – Respiratory, Glenfield Hospital Esler, Colin; University Hospitals of Leicester NHS Trust, Orthopaedics, Leicester General Hospital Singh, Sally; University Hospitals of Leicester NHS Trust, Centre for Exercise and Rehabilitation Sciences, NIHR Leicester Biomedical Research Centre – Respiratory, Glenfield Hospital; University of Leicester, Department of Respiratory Sciences
<b>Primary Subject Heading</b>:	Rehabilitation medicine
Secondary Subject Heading:	Rehabilitation medicine
Keywords:	Knee < ORTHOPAEDIC & TRAUMA SURGERY, Rehabilitation medicine < INTERNAL MEDICINE, Musculoskeletal disorders < ORTHOPAEDIC & TRAUMA SURGERY

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3 **Figure 1. Flow diagram of study procedures**  
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Figure.2 NMES Device Footplate  
159x158mm (72 x 72 DPI)



Figure.3 NMES Quadriceps Electrodes

264x148mm (96 x 96 DPI)

## SUPPLEMENTARY MATERIAL

### 36-Item Short Form Survey (SF-36)

The SF-36 is a non-disease specific health related quality of life measure developed as part of the Medical Outcome Study (MOS). The SF-36 is self-administered and measures 8 domains of health status; physical functioning, physical role limitations, emotional role limitations, pain, general health perceptions, energy/vitality, social functioning and mental health.

### EuroQol 5-Dimension 5-Level health questionnaire (EQ-5D-5L)

The EQ-5D-5L is a non-disease specific health related quality of life measure developed by the EuroQol group. The EQ-5D-5L is self-administered and measures health 5 dimensions (mobility, self-care, usual activities, pain or discomfort, and anxiety or depression) and uses a visual analogue score to measure health today on a scale from 0 to 100

### Medical Outcome Study Sleep Scale (MOS Sleep)

The MOS Sleep is a sleep measure developed as part of the Medical Outcome Study (MOS). The questionnaire is self-administered and assesses 12 items; sleep disturbance, sleep adequacy, somnolence, quantity of sleep, snoring, and awakening short of breath or with a headache.

### Hospital Anxiety and Depression Score (HADS)

The HADS is a self-administered questionnaire comprising of seven questions for anxiety and seven questions for depression. Anxiety and depression scores are calculated independently and are categorised in the following thresholds: 8–10 mild, 11–14 moderate, 15–21 severe. For both scales, scores of less than 7 indicate non-cases.

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### Footplate Stimulation Programme and Parameters

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Mode	Phase Duration (µs)	Basic Wave Frequency (kHz)	Frequency (Hz)	On Duration (s)	Off Duration (s)	Voltage (V) (Level=99)	Current (mA) (Level=99)	Voltage (V) (Level=50)	Current (mA) (Level=50)
Tolerance	±10%	±10%	±10%	±10%	±10%	±15%	±15%	±15%	±15%
1	450	1.4	20.0	3.2	1.0	70	10.1	43	6.4
2	450	1.4	25.0	6.9	1.0	69	11.3	42	7.4
3	450	1.4	38.8	4.4	1.0	66	12.9	41	8.2
4	450	1.4	35.7	7.1	1.0	67	12.8	41	8.1
5	450	1.4	32.5	4.4	1.5	67	12.7	40	7.9
6	450	1.4	32.4	4.6	1.0	67	12.6	40	7.9
7	970	1.0	35.6	1.9	1.5	52	14.0	34	9.7
8	450	1.4	25.3	4.3	1.5	70	11.4	43	7.4
9	450	1.4	32.5	7.8	1.0	68	12.5	40	7.7
10	450	1.4	43.7	8.3	1.0	63	13.6	37	8.3
11	450	1.4	31.3	2.2	1.5	68	12.4	40	7.7
12	450	1.4	43.6	5.5	1.0	63	13.4	37	7.9
13	450	1.4	43.7	4.6	1.0	67	12.6	40	7.9
14	450	1.4	37.6	4.2	1.0	66	13.2	41	8.3
15	450	1.4	43.7	5.0	1.0	62	13.5	37	8.3

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8 **Quadriceps Stimulation Programme and Parameters**  
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Mode	Phase Duration ( $\mu$ s)	Basic Wave Frequency (kHz)	Frequency (Hz)	On Duration (s)	Off Duration (s)	Voltage (V) (Level=99)	Current (mA) (Level=99)	Voltage (V) (Level=50)	Current (mA) (Level=50)
Tolerance	$\pm 10\%$	$\pm 10\%$	$\pm 10\%$	$\pm 10\%$	$\pm 10\%$	$\pm 15\%$	$\pm 15\%$	$\pm 15\%$	$\pm 15\%$
1	450	1.4	32.5	33	27	65.2	12.2	41.2	8.14
2	450	1.4	32.5	13	17	65.2	12.2	41.2	8.14



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	Addressed on page number
<b>Administrative information</b>			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	___ 1 ___
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	___ 3-4 ___
	2b	All items from the World Health Organization Trial Registration Data Set	___ Complete ___
Protocol version	3	Date and version identifier	___ 2 ___
Funding	4	Sources and types of financial, material, and other support	___ 21 ___
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	___ 1 ___
	5b	Name and contact information for the trial sponsor	___ 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	___ 20 ___
	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)	___ 20 ___

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1	<b>Introduction</b>			
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3	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	___ 5-8 ___
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6		6b	Explanation for choice of comparators	___ 5-8 ___
7				
8	Objectives	7	Specific objectives or hypotheses	___ 7-8 ___
9				
10	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)	___ 8 ___
11				
12				
13				
14	<b>Methods: Participants, interventions, and outcomes</b>			
15				
16	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	___ 8 ___
17				
18				
19	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)	___ 9-10 ___
20				
21				
22	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	___ 11-13 ___
23				
24		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)	___ 13 ___
25				
26		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	___ 13 ___
27				
28		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	___ 10 ___
29				
30	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	___ 14-16 ___
31				
32				
33				
34	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 ___
35				
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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	8-9
2				
3				
4	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	9
5				
6	<b>Methods: Assignment of interventions (for controlled trials)</b>			
7	<b>Allocation:</b>			
8				
9				
10	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	11
11				
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16	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	11
17				
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20	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	11
21				
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23				
24	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	11
25				
26				
27		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	11
28				
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30				
31	<b>Methods: Data collection, management, and analysis</b>			
32				
33	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	14-16
34				
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39		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	12
40				
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1	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	_____18_____
2				
3				
4				
5	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	_____18-19_____
6				
7				
8		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	_____18-19_____
9				
10		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)	_____18-19_____
11				
12				
13				
14	<b>Methods: Monitoring</b>			
15				
16	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	_____20_____
17				
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21				
22		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	_____8_____
23				
24				
25	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	_____11_____
26				
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28	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	_____20_____
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32	<b>Ethics and dissemination</b>			
33				
34	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	_____19_____
35				
36				
37	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)	_____20_____
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1	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	_____ 3 _____
2				
3				
4		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	_____ N/A _____
5				
6				
7	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	_____ 18, 20 _____
8				
9				
10	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	_____ 19-20 _____
11				
12				
13	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	_____ 20 _____
14				
15				
16	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	_____ 11 _____
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19				
20	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	_____ 3, 11, 19 _____
21				
22				
23				
24		31b	Authorship eligibility guidelines and any intended use of professional writers	_____ N/A _____
25				
26		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	_____ N/A _____
27				
28				
29	<b>Appendices</b>			
30				
31	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	_____ Attached _____
32				
33				
34	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	_____ N/A _____
35				
36				

\*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.

# 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

Journal:	<i>BMJ Open</i>
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<b>Primary Subject Heading</b>:	Rehabilitation medicine
Secondary Subject Heading:	Rehabilitation medicine
Keywords:	Knee < ORTHOPAEDIC & TRAUMA SURGERY, Rehabilitation medicine < INTERNAL MEDICINE, Musculoskeletal disorders < ORTHOPAEDIC & TRAUMA SURGERY



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3 1 **Effects of combining electrical stimulation of the calf and thigh muscles in patients with**  
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6 2 **osteoarthritis of the knee: protocol for a double-blind, randomised, sham-controlled trial**  
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8  
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58  
59 21 Word Count: 3310  
60

1  
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3 22 Keywords: Knee, Osteoarthritis, Electrical Stimulation  
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10 24 **ABSTRACT**  
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13 25 **Introduction**  
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16 26 Knee osteoarthritis (KOA) is a leading cause of disability and is characterised by  
17  
18 27 degenerative changes causing pain and loss of function. Neuromuscular electrical  
19  
20 28 stimulation (NMES) has been shown to influence muscle size and strength in healthy  
21  
22 29 subjects. A novel self-administered NMES device has been developed to help manage the  
23  
24 30 symptoms of KOA. This study aims to investigate the effects of combining NMES of the calf  
25  
26 31 and quadriceps on individuals with KOA.  
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31

32 32 **Methods and analysis**  
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35 33 193 individuals with KOA will be recruited to a single-centre, double-blind, randomised,  
36  
37 34 sham-controlled trial at the Respiratory Biomedical Research Centre, Leicester, United  
38  
39 35 Kingdom. Participant will be randomised (1:1) to follow an 8-week home-based intervention  
40  
41 36 using a NMES device or sham device. The NMES device consists of footplate electrodes and  
42  
43 37 two quadriceps electrodes. Footplate stimulation will be completed daily for 30 minutes and  
44  
45 38 quadriceps stimulation for 20 minutes, 5 times a week (compliance is recorded in a self-  
46  
47 39 reported participant diary). The primary outcome is the Western Ontario and McMaster  
48  
49 40 Universities Arthritis Index (WOMAC) pain domain, taken at 8 weeks follow up. Secondary  
50  
51 41 outcomes will explore quadriceps muscle strength, swelling, health-related quality of life,  
52  
53 42 exercise capacity, anxiety and depression, sleep, physical activity and self-reported  
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55 43 compliance. A powered subgroup analysis for compliance to the active device will be  
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3 44 complete for the primary outcome. Participant focus groups will be completed following  
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5 45 recruitment of half of the participants and after all participants have been recruited.  
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#### 9 46 **Ethics and dissemination**

10  
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12 47 Ethical approval has been obtained from the North-West Preston ethics committee  
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14 48 (17/NW/0081). Participants are required to provide informed consent following review of  
15  
16  
17 49 the participant information sheet and discussion regarding study procedures with a member  
18  
19  
20 50 of the research team. The study results will be disseminated to the appropriate stakeholders  
21  
22 51 through presentations, conferences and peer-reviewed journals. Results will be presented  
23  
24 52 to participants following study completion at the Biomedical Research Centre – Respiratory,  
25  
26  
27 53 Glenfield Hospital, Leicester.  
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#### 30 54 **Trial registration number**

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33 55 ISRCTN registry, ISRCTN12112819 (date registered 01/05/2019). IRAS registry 219693.  
34  
35  
36 56 University Hospitals of Leicester registry 91017. Protocol Version 8.  
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#### 42 58 **Strengths and limitations of this study**

- 43  
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45 59
- 46 • This study protocol describes a double-blind, randomised, sham-controlled trial  
47  
48 60 investigating neuromuscular electrical stimulation (NMES) for individuals with  
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50 61 osteoarthritis of the knee.  
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  - 53 62 • This protocol includes a powered (80%) subgroup analysis for compliance to the  
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55 63 active device.  
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3 64           • The protocol includes focus groups to understand the participant experience of  
4  
5                using NMES for osteoarthritis of the knee.  
6 65  
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8 66           • One limitation of the study is that compliance is measured through self-reported  
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10             diaries and is not an embedded function of the device.  
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## 69 INTRODUCTION

70 Osteoarthritis (OA) is the most common form of arthritis and is one of the leading causes of  
71 disability globally [1]. In the United Kingdom, 23% of people aged 45 years or older are  
72 estimated to have OA with the knee being the most commonly affected joint [2]. Knee  
73 osteoarthritis (KOA) is associated with increased comorbidities and higher mortality rates [3,  
74 4]. OA is also associated with increased healthcare utilisation leading to a significant  
75 economic burden [5].

76 KOA is driven by a combination of biomechanical and proinflammatory factors causing  
77 changes within the joint and periarticular muscles [6]. Muscular weakness is associated with  
78 structural degradation and symptom development in KOA [7, 8]. Exercise is effective for  
79 improving pain and physical function in KOA and is recommended in national guidelines [9,  
80 10]. Importantly, strengthening the periarticular knee muscles is proposed to stabilise the  
81 joint, improve shock attenuation and influence underlying inflammatory pathways involved  
82 in KOA. Although exercise is recommended, barriers such as pain, self-efficacy and impaired  
83 general health status can impact adherence [11, 12]. Other factors such as social isolation  
84 and depression are also common in OA populations leading to further challenges in  
85 engaging with prescribed exercise programmes [13, 14]. In addition, the pain relieving effect



1  
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3 86 of exercise interventions decreases over time [9]. Therefore finding an accessible modality  
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5  
6 87 that targets both pain and the muscular deficits seen in KOA is desirable.  
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9 88 Neuromuscular electrical stimulation (NMES) provides superficial stimulation to the muscle  
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11 89 and generates an alternate activation pattern compared to voluntary contraction [15].  
12

13  
14 90 NMES uses low amplitude electrical pulses to stimulate motor neurons and induce muscular  
15  
16 91 contraction. This may be important for pathologies such as KOA where arthrogenic muscle  
17  
18 92 inhibition has been proposed [16]. NMES has been shown to achieve improvements in the  
19  
20 93 knee extensor strength through neural and muscular adaptations [17, 18]. A systematic  
21  
22 94 review found NMES to be effective for improving isometric strength in KOA and to be an  
23  
24 95 appropriate treatment in addition to exercise programmes [19]. NMES achieves consistently  
25  
26 96 high adherence ranging from 81% - 91% for individuals with KOA and is considered a low risk  
27  
28 97 intervention [20-22]. The post-treatment pain relief experienced while using NMES within  
29  
30 98 the parameters for muscle strengthening may contribute to the high adherence rates [20,  
31  
32 99 22].  
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39 100 Due to the current quality of evidence the clinical validity of isolated NMES of the  
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41 101 quadriceps for symptomatic KOA remains unclear [23]. Previous trials exploring the effect of  
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43 102 NMES for KOA have utilised a wide range of stimulation parameters and training frequencies  
44  
45 103 [19]. In addition, previous research frequently combines NMES with exercise or other  
46  
47 104 modalities; therefore it is difficult to determine the unique impact of NMES from a  
48  
49 105 multifaceted intervention. This has caused significant variability in results with regards to  
50  
51 106 quadriceps strengthening and associated pain relief. Challenges for NMES prescription  
52  
53 107 include individualising the stimulation intensity to individual tolerance whilst aiming to  
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55 108 achieve sufficient stimulation to produce physiological adaptations. Progression of NMES  
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3 109 intensity is important during an NMES programme as individuals become habituated to the  
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6 110 sensation. Progressing intensity recruits additional muscle fibres at a greater distance from  
7  
8 111 the electrode site increasing the potential area for muscular adaptation [24].  
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10  
11 112 NMES investigations frequently include targeting isolated muscle groups in the treatment of  
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13  
14 113 KOA [20-22, 25]. Muscle deficits are most frequently reported in the knee extensors  
15  
16 114 compared to the surrounding muscle groups in KOA, although strength deficits are seen  
17  
18 115 throughout the lower limb [26]. Compared to healthy controls, individuals with KOA present  
19  
20  
21 116 with weakness and altered activation patterns in the plantarflexors [27-29]. Both the knee  
22  
23 117 extensors and plantarflexors are important muscle groups involved in propulsion during the  
24  
25  
26 118 gait cycle. Walking speed is a predictor of function and mortality in older adults and slower  
27  
28 119 walking speed is associated with KOA [30]. NMES has been shown to be an effective  
29  
30  
31 120 intervention for increasing strength in the plantarflexors in healthy populations [31]. To the  
32  
33 121 authors knowledge there have been no previous investigations into calf and foot NMES in  
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35  
36 122 the KOA population. It is unknown if stimulating several muscle groups around the knee will  
37  
38 123 provide superior pain relief and functional performance for individuals with KOA.  
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40  
41 124 An NMES device (Revitive Arthritis Knee®) has been developed to improve lower limb  
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44 125 strength, function, swelling and pain in individuals with KOA. Unlike previous NMES devices,  
45  
46 126 the device provides stimulation to the musculature of the knee both proximally and distally.  
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48  
49 127 The device consists of electrodes for quadriceps stimulation and footplate electrodes for  
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51 128 stimulation of the calf and foot. The footplate has previously been investigated for its  
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54 129 influence on peripheral artery disease and chronic venous disease and was found to  
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56 130 significantly improve circulation and walking distance [32, 33]. These investigations did not  
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3 131 include quadriceps stimulation and there have been no investigations into the effects of the  
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6 132 device for KOA.  
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9 133 The objectives for the trial are: 1) to determine the effects of a NMES device on pain,  
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11 134 strength, swelling, health related quality of life, sleep, anxiety, depression, exercise capacity  
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14 135 and physical activity in participants with symptomatic KOA when compared with a sham  
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16 136 device; 2) to conduct a subgroup analysis (per protocol) based on compliance, self-  
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18 137 administered stimulation intensity, baseline pain and function and knee extensor strength  
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20  
21 138 to explore if there is a subgroup of patients who receive the most benefit from NMES 3) to  
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23  
24 139 conduct focus groups to explore participant experiences of using a NMES device for the  
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26 140 management of KOA. The trial hypothesis is an expected 20% difference in the primary  
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28 141 outcome (WOMAC pain) at 8 weeks between groups in favour of the active device.  
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## 33 34 35 143 **METHODS AND ANALYSIS**

### 36 37 38 144 **Trial design and registration**

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41 145 This is a single-centre, double-blind, sham controlled, randomised superiority trial of NMES  
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44 146 in KOA. The primary outcome is the Western Ontario and McMaster Universities  
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46 147 Osteoarthritis Index (WOMAC) pain domain [34]. The trial is registered on the ISRCTN  
48  
49 148 website (ISRCTN12112819). All trial procedures will be completed at the Centre for Exercise  
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51 149 and Rehabilitation Science, NIHR Leicester Biomedical Research Centre – Respiratory,  
52  
53  
54 150 Glenfield Hospital, Groby Road, Leicester, LE3 9QP, UK. Participant visits and the order of  
55  
56 151 outcome measures are described in figure 1.  
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## 153 **Participants**

154 The sample size was calculated to detect a 20% difference (SD=19) between groups using a  
155 significance level of 0.05 for the WOMAC pain domain with 90% power. This requires 62  
156 participants to complete the protocol (n=31 in each group). An expected drop-out rate of  
157 30% was predicted, requiring 80 participants in total. In addition, the required recruitment  
158 to provide statistical power for the WOMAC pain domain for compliant participants in the  
159 active arm was prospectively calculated. Compliance is defined as completing 20 minutes of  
160 quadriceps stimulation 3 times per week for each of the 8 weeks. A pre-planned analysis of  
161 compliance data was performed following the completion of the first 50 participants. An  
162 unblinded reviewer (SBP) observed the active group compliance data only. The compliance  
163 level for the active group was 63%. Therefore, a total of 128 participants would be required  
164 to be recruited in each arm to allow a powered subgroup analysis for a compliant group  
165 within the active arm.

166 Due to COVID-19 restrictions 33 participants were unable to attend the study site and  
167 complete visit 3 exercise testing and physical assessments. Therefore an additional 33  
168 participants will be recruited to account for the altered study engagement in these  
169 participants. To account for expected study engagement during the COVID-19 pandemic, the  
170 sample size was increased by 20%. In total, 193 participants will be recruited to the trial.

171 Participants will be recruited from outpatient physiotherapy clinics, orthopaedic out-patient  
172 clinics, sports and exercise medicine outpatient clinics and primary care (General Practice;  
173 GP) registers. Participants will be identified as eligible if they:

- 1  
2  
3 174 • KOA diagnosed in accordance with National Institute for Health and Care Excellence  
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5  
6 175 (NICE) guidelines [35]  
7  
8 176 NICE diagnostic criteria: individual is 45 or over, has activity-related joint pain and  
9  
10 177 has either no morning joint-related stiffness or morning stiffness that lasts no longer  
11  
12 178 than 30 minutes; KOA is diagnosed clinically without requiring radiographic  
13  
14 179 investigations  
15  
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18 180 • Aged 45-85 years  
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20

21 181 Individuals are excluded from participating in the trial if they are:  
22

- 23  
24 182 • Fitted with an electronic implant such as a pacemaker or defibrillator  
25  
26  
27 183 • Pregnant  
28  
29  
30 184 • Existing or undergoing treatment for a DVT  
31  
32 185 • Significantly impaired cognitive ability  
33  
34  
35 186 • Have inflammatory arthritis  
36  
37 187 • Have a dermatological condition affecting the feet or legs  
38  
39  
40 188 • Have a neurological disorder affecting the feet or legs  
41  
42 189 • Have osteoarthritis of the hip, ankle or foot effecting mobility more than the  
43  
44 190 effected knee  
45  
46  
47 191 • Current or recent knee surgery or injury in the last 3 months  
48  
49  
50 192 • Had a total knee replacement, partial knee replacement or high tibial osteotomy on  
51  
52 193 the knee to be studied  
53  
54  
55 194 • Had a corticosteroid or hyaluronic acid injections in the last 6 months  
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57  
58 195 • BMI over or equal to 40  
59  
60 196 • Completing a concomitant physiotherapy programme

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2  
3 197 • Current use of transcutaneous electrical nerve stimulation (TENS)  
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6 198 • Current or previous use of neuromuscular stimulation device  
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8 199 • Unable to mobilise  
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11 200 • Inability to provide informed consent  
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14 201

## 17 202 **Randomisation**

20 203 Participants will complete a consent form at the study site during visit 1 and participants  
21  
22  
23 204 must consent to be randomised to either arm of the study. The study consent form is  
24  
25 205 provided in the supplementary material. Participants will be randomised at visit 2 using an  
26  
27  
28 206 online randomisation tool ([www.sealedenvelope.com](http://www.sealedenvelope.com)). Participants are randomised (1:1) to  
29  
30 207 an active or sham device. Group allocation will be concealed from both the participant and  
31  
32 208 the blinded assessors. Active and sham devices are provided in identical boxes and are  
33  
34  
35 209 closely matched in design. Unblinding is permissible in cases of medical emergencies. All  
36  
37  
38 210 adverse events occurring after randomisation to the study and until the final postal follow  
39  
40 211 up will be recorded and reported to the study sponsor.  
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## 46 213 **Patient and public involvement**

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49  
50 214 When developing the trial protocol, a patient and public involvement (PPI) meeting was  
51  
52 215 conducted to discuss the feasibility of the intervention and trial visits. Advice from PPI  
53  
54  
55 216 members provided guidance on explaining participant randomisation, administering the  
56  
57 217 device and the format of the participant diaries. Following completion of the trial,  
58  
59 218 participants will be offered the opportunity to attend study steering committee meetings.

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3 219 They will have the opportunity to provide feedback on the trial and guide trial management.  
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5 220 Following data analysis, participants will be invited to a dissemination event at the  
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7  
8 221 Biomedical Research Centre – Respiratory, Glenfield Hospital, Leicester.  
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15 223 **Intervention**

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18 224 The NMES device footplate (Figure. 2) provides a 30 minute programme of pulsed current  
19

20 225 with 15 different preprogramed biphasic waveform patterns. Each pattern lasts  
21

22 226 approximately 1 minute with the 15 minute cycle complete twice over the 30 minute  
23

24 227 session. The modulated output with description of frequency, pulse duration, duty cycle  
25

26 228 (on/off duration) and mid/peak values for voltage and current are described in the  
27

28 229 supplementary material. The footplate electrodes require direct contact with the skin and  
29

30 230 provide bilateral stimulation to the calf and foot. The footplate contains an *IsoRocker* on the  
31

32 231 base which allows the device to pivot at an angle of 15 degrees permitting plantarflexion of  
33

34 232 the ankle during stimulation. Participants are instructed to use the 30 minute footplate  
35

36 233 stimulation programme 7 days a week.  
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43 234 The quadriceps stimulation consists of two 10x12.5cm self-adhesive electrodes for  
44

45 235 unilateral stimulation (Figure. 3). The quadriceps electrodes are placed proximally to rectus  
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47 236 femoris motor point and distally covering the vastus medialis motor point [36]. The  
48

49 237 quadriceps electrodes provide two patterns of stimulation allowing users to familiarise with  
50

51 238 the sensation before entering into a second phase of the strengthening protocol. The  
52

53 239 quadriceps stimulation programme lasts 20 minutes and is detailed in the supplementary  
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3 240 material. Participants are instructed to use the 20-minute quadriceps stimulation  
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5  
6 241 programme 5 times per week.  
7  
8  
9 242 Both the footplate and quadriceps stimulation are performed in a seated position.  
10  
11 243 Stimulation is provided in isolation to either the footplate or quadriceps electrodes.  
12  
13  
14 244 Participants are advised to use the footplate and quadriceps stimulation programme in  
15  
16 245 succession during the 5 days each week of completing both programmes. Intensity is  
17  
18 246 displayed on the footplate and ranges from 0 to 99. Intensity is adjusted through the  
19  
20 247 footplate display or remote control. The device contains a stimulation timer which descends  
21  
22 248 once the programme has started. To achieve optimum stimulation intensity participants are  
23  
24 249 guided by a researcher to achieve a strong muscular contraction during visit 2. They are  
25  
26 250 instructed to progress the intensity on a daily basis as tolerated. Use of the device and peak  
27  
28 251 stimulation intensity achieved each session is recorded in a participant reported diary  
29  
30 252 provided during visit 2.  
31  
32  
33  
34  
35  
36 253 The sham device footplate and stimulation pads appear indistinguishable from the active  
37  
38 254 device. The sham device is operationally identical including remote activation and control.  
39  
40 255 The sham device voltage and current is limited to ensure no muscular contraction. When  
41  
42 256 demonstrating the sham device the unblinded researcher will inform the participant that it  
43  
44 257 is expected and normal to not experience a sensation. Participants will have no prior  
45  
46 258 experience of using NMES and will therefore be unable to distinguish between active and  
47  
48 259 sham devices. If a participant is unblinded by information external to the study this will be  
49  
50 260 recorded and they will be asked to continue to complete their 8-week post intervention  
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52 261 assessment.  
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3 262 Participants will receive a telephone call from an unblinded member of the research team  
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6 263 four weeks into the intervention phase. This will provide an opportunity to answer any  
7  
8 264 participant queries, encourage adherence to the intervention and prompt progression of  
9  
10 265 stimulation intensity.

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14 266 Participants and the visit 3 assessor will remain blinded to the intervention group  
15  
16 267 throughout the trial. After completing visit 3, participants who have received the sham  
17  
18 268 device will be provided with the active device by the unblinded personnel. Following visit 3,  
19  
20 269 participant's continued use of the device is optional and they are not instructed to follow a  
21  
22 270 specific NMES programme.

### 271 **Outcome measures**

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

### 277 **Primary outcome – Western Ontario and McMaster Universities Arthritis Index (WOMAC)** 278 **(Pain Domain)**

279 The WOMAC is a disease specific questionnaire consisting of 24 questions within 3 domains;  
280 pain, stiffness and function [34]. Each domain consists of a 0-4 Likert scale with lower score  
281 indicating less severe symptoms or disability. The WOMAC has acceptable reliability and  
282 validity in individuals with KOA [37].

1  
2  
3 283 The primary outcome is the WOMAC pain domain administered prior to the intervention  
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5  
6 284 and following the 8-week intervention phase. The WOMAC questionnaire is also sent to  
7  
8 285 participants 16 weeks after randomisation via postal follow up. The primary end point is 8  
9  
10 286 weeks following randomisation.

### 14 287 **Self-reported knee pain, function and stiffness**

16  
17 288 Participants will complete the WOMAC and Oxford Knee score [38]. The Oxford Knee score  
18  
19 289 comprises of 12 equally weighted questions addressing the patient's perceived pain and  
20  
21  
22 290 functional ability on a Likert scale with values form 0 to 4, with a reference range of the last  
23  
24 291 4 weeks. The total score ranges from 0 to 48 and is categorised in the following thresholds:  
25  
26  
27 292 0-19 severe, 20-29 moderate-severe, 30-39 mild-moderate and 40-48 satisfactory pain.

### 30 293 **Health questionnaires**

31  
32  
33 294 Health status will be measured by the 36-Item Short Form Survey (SF-36) [39], EuroQol 5-  
34  
35 295 Dimension 5-Level health questionnaire (EQ-5D-5L) [40], Medical Outcome Study Sleep  
36  
37 296 Scale (MOS Sleep) [41] and Hospital Anxiety and Depression Score (HADS) [42]. Details of  
38  
39  
40 297 each measure are provided in the supplementary material.

### 44 298 **Exercise capacity**

45  
46  
47 299 Exercise capacity will be measured using the Incremental Shuttle Walk Test (ISWT) [43] and  
48  
49 300 Endurance Shuttle Walk Test (ESWT) [44]. Each participant will complete a familiarisation  
51  
52 301 ISWT on visit 2, the ISWT is then repeated following 30 minutes allowing heart rate and  
53  
54 302 blood pressure to return to pre-exercise levels. The ESWT walking speed is calculated based  
55  
56  
57 303 on 80%-85% of the maximum ISWT score. Both the ISWT and ESWT will be completed at  
58  
59 304 visit 2 and visit 3.

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3 305 **Knee extensor strength**  
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6 306 The knee extensor strength test is performed seated with 90 degrees hip and knee flexion  
7  
8  
9 307 using an isokinetic dynamometer (Cybex NORM II, CSMi, Stoughton, USA). Knee extensor  
10  
11 308 strength will be measured through 5 x 10 second maximal voluntary isometric contractions  
12  
13  
14 309 with 60 second rest periods between repetitions. The highest score achieved during  
15  
16 310 strength testing will be used for analysis. Prior to maximal strength testing participants will  
17  
18 311 complete 3 x 5 second submaximal isometric contractions with 60 second rest periods  
19  
20  
21 312 between repetitions as a warm-up.  
22  
23

24 313 **Swelling**  
25  
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27 314 Swelling of the knee and ankle will be assessed through joint line circumference  
28  
29 315 measurements of the knee and ankle at week 0 and week 8 using a flexible tape measure.  
30  
31 316 Three measurements will be taken and the mean calculated. Measurements will be taken  
32  
33 317 prior to randomisation and repeated by a blinded assessor on visit 3. Circumference  
34  
35 318 measurements of the knee have been shown to achieve high levels of inter-rater reliability  
36  
37  
38 319 [45].  
39  
40  
41  
42

43 320 **Physical activity**  
44  
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46 321 Participants will wear an ActiGraph GT3X activity monitor (ActiGraph, Pensacola, FL, USA)  
47  
48 322 during waking hours for 7 days between visit 1 (week 0) and visit 2 (week 1). Participants  
49  
50 323 will also wear the device during waking hours for 7 days prior to visit 3. The ActiGraph GT3X  
51  
52 324 activity monitor cannot be worn during water based activities. Physical activity data will be  
53  
54 325 analysed using ActiLife software (Actigraph).  
55  
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## 327 **Compliance**

328 Compliance for both groups is defined as completing 20 minutes of quadriceps stimulation 3  
329 times per week for each of the 8 weeks. Compliance to the intervention for both groups will  
330 be recorded in a self-reported participant diary provided at visit 2. The diary will record the  
331 date of use, time of use, stimulation location ('thigh pads' or 'footplate'), duration of use  
332 and peak intensity level achieved. There will also be a section provided for participants to  
333 record any changes in pain medication, activity levels, health status or other health care  
334 interventions.

## 335 **Qualitative focus groups**

336 Focus groups will be completed following recruitment of half the trial participants (n=80)  
337 and following recruitment of all participants (n=160). A mid-recruitment focus group has  
338 been selected to reduce the recall period for participants who were recruited prior to the  
339 mid-point. The focus groups will aim to understand the experience of using NMES for the  
340 management of KOA. This includes the factors impacting compliance during and after the  
341 trial. Each focus group will include approximately 8 participants. All participants from both  
342 sham and active groups who consent to be contacted will be invited to participate in the  
343 focus groups. The sham group will have experience using NMES after being provided the  
344 active device following completion of the trial. The focus groups will be conducted in person  
345 in a hospital setting or virtually by a member of the research team. A researcher diary will  
346 be kept for purposes of reflexivity and to support data analysis and theme development.

## 347 **Data analysis plan**

1  
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3 348 Data collected will be entered into a secure online database 'Research Electronic Data  
4  
5  
6 349 Capture' (REDCap) [46. 47] by authorised members of the researcher team. Prior to analysis  
7  
8 350 a study data check will be completed by a second study researcher. Baseline characteristics  
9  
10 351 will be described and group comparison will be analysed using an independent t-test or non-  
11  
12 352 parametric test. An intention to treat analysis will be completed. Changes in all outcomes  
13  
14 353 will be described pre and post intervention and analysed using paired t-test's or non-  
15  
16 354 parametric equivalent, the primary outcome being the WOMAC pain domain at 8 weeks.  
17  
18 355 Differences between time points and groups will be compared using repeated measures  
19  
20 356 ANOVA. Baseline scores will be included as covariates within the ANOVA analysis to account  
21  
22 357 for any significant differences. The WOMAC questionnaire will also be compared between  
23  
24 358 groups at the 16 week time point. An analysis of 'responders' and 'non-responders' will be  
25  
26 359 explored for all outcomes following data collection. Responders are defined as participants  
27  
28 360 who achieve a 20% improvement in the primary outcome during the 8-week intervention  
29  
30 361 phase.

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38 362 Pre-defined subgroup analyses will be performed on: 1) compliant versus non-compliant  
39  
40 363 (compliance defined within compliance section above) a per protocol analysis, 2)  
41  
42 364 participants who were able to attend the study site prior to and following COVID-19 study  
43  
44 365 site attendance restrictions 3) recruitment source (e.g orthopaedic clinics, physiotherapy  
45  
46 366 clinics, GP Registers). Further exploratory analyses will be performed on physical activity  
47  
48 367 measures.

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52  
53 368 Qualitative focus groups will be transcribed verbatim and analysed through NVivo version  
54  
55 369 12 (QSR International) using thematic analysis [48]. The main themes generated from the  
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3 370 analysis will be discussed with participants of the focus groups to ensure the discussion was  
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6 371 represented accurately.  
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## 12 373 **ETHICS AND DISSEMINATION**

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15 374 Ethical approval was provided by the North-West Preston Research Ethics Committee on the  
16  
17  
18 375 22<sup>nd</sup> February 2017 (17/NW/0081). Participants provided informed consent following review  
19  
20  
21 376 of the participant information sheet and discussion regarding study procedures with a  
22  
23 377 member of the research team. Findings from the trial will indicate the clinical effectiveness  
24  
25 378 of this NMES device. Conduct of the trial began on 13/05/2019 and the data collection will  
26  
27  
28 379 be completed within 2022. These findings will be disseminated in line with the Centre for  
29  
30 380 Exercise and Rehabilitation Science dissemination strategy and will be submitted for  
31  
32  
33 381 publication in a peer-reviewed journal.  
34  
35

36 382 Dissemination will be completed to participants of the trial and more broadly to health care  
37  
38 383 professionals, patients, members of the public and academics. The results of the study will  
39  
40 384 be presented at regional and national musculoskeletal conferences.COVID-19  
41  
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43

44 385 Due to the ongoing COVID-19 pandemic, the protocol procedures may be altered as  
45  
46 386 necessary for participant safety. Any adaptations will be discussed in the publication of the  
47  
48  
49 387 study and via ISRCTN.  
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51

## 52 388 **COMPOSITION, ROLES, AND RESPONSIBILITIES**

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55 389 Trial processes and data is managed and audited within the University Hospitals of Leicester.  
56  
57  
58 390 The study sponsor (Actegy Ltd) will have access to anonymised trial data following the  
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60

1  
2  
3 391 completion of all data collection. Trial analysis will be completed by the research team  
4  
5  
6 392 within University Hospitals of Leicester or an independent statistician.  
7  
8

9 393 **PROTOCOL MODIFICATIONS**

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12 394 Trial registries, research ethics committee, study sponsor and participants will be informed  
13  
14 395 of any protocol modifications by a member of the study team from University Hospitals of  
15  
16  
17 396 Leicester.

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20 397 **PRIMARY TRIAL SPONSOR**

21  
22  
23 398 Actegy Ltd (Bracknell, UK).  
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33 401 **CONTRIBUTORS**

34  
35  
36 402 SS is the principal investigator of the research trial. SS, SBP, LHW, ED, LL, CE were involved in  
37  
38 403 the development of the intervention and design of the trial. SS, SBP, LHW, ED, LL, CE, CG,  
39  
40 404 GM have been involved in drafting the work or revising it critically for important intellectual  
41  
42 405 content and have given the final approval of the version published.  
43  
44  
45  
46

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49  
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51  
52 408 (219693).  
53  
54  
55

56 409 **COMPETING INTERESTS**

57  
58  
59 410 S. Singh reports grants from Actegy Ltd during the conduct of the study.  
60

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413

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58 566 **Figure titles**  
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568 **Figure 1. Flow diagram of study procedures**

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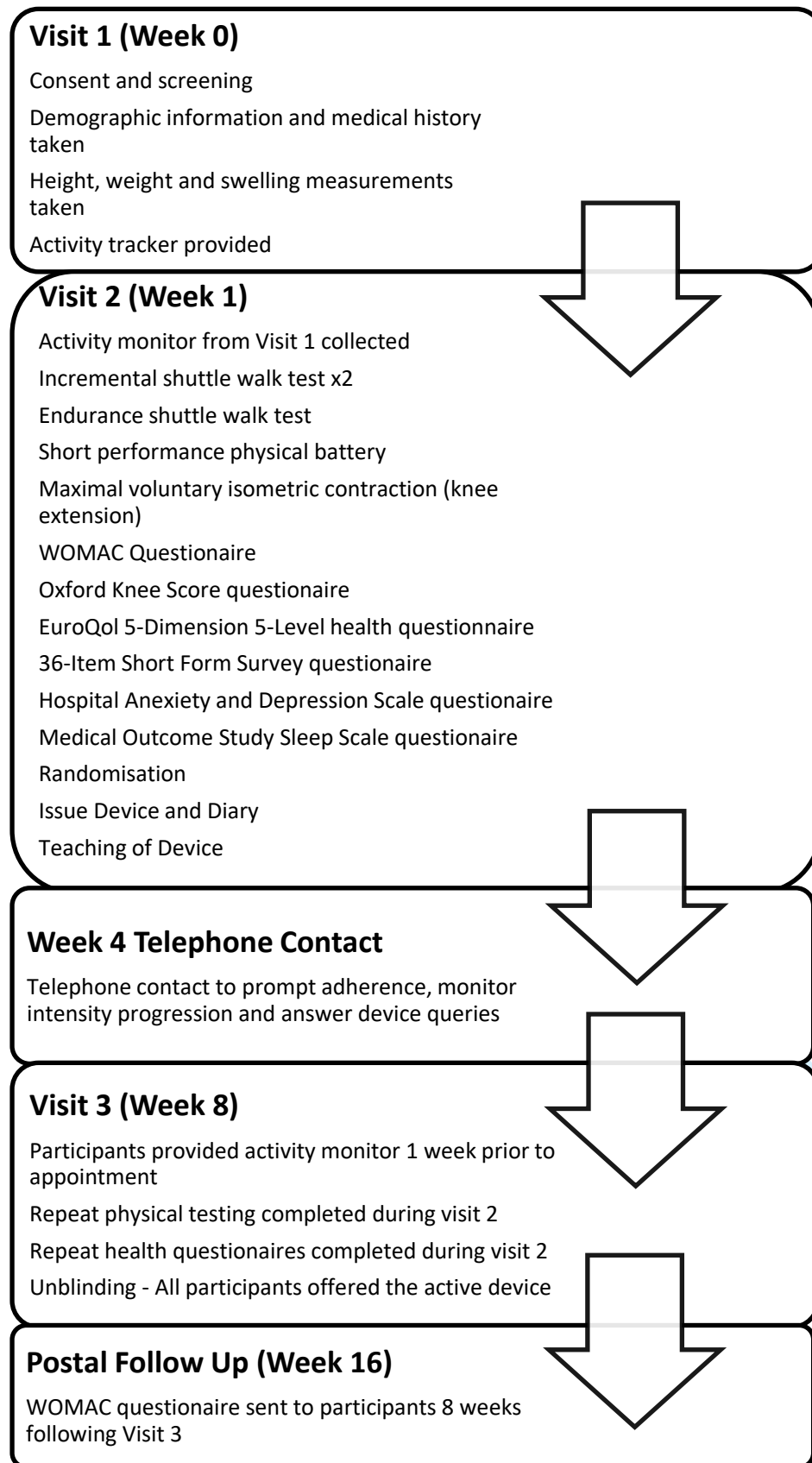
570 **Figure 2. NMES Device Footplate**

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572 **Figure 3. NMES Quadriceps Electrodes**

For peer review only

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3 **Figure 1. Flow diagram of study procedures**  
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Figure.2 NMES Device Footplate  
159x158mm (72 x 72 DPI)



Figure.3 NMES Quadriceps Electrodes

264x148mm (96 x 96 DPI)

## SUPPLEMENTARY MATERIAL

### 36-Item Short Form Survey (SF-36)

The SF-36 is a non-disease specific health related quality of life measure developed as part of the Medical Outcome Study (MOS). The SF-36 is self-administered and measures 8 domains of health status; physical functioning, physical role limitations, emotional role limitations, pain, general health perceptions, energy/vitality, social functioning and mental health.

### EuroQol 5-Dimension 5-Level health questionnaire (EQ-5D-5L)

The EQ-5D-5L is a non-disease specific health related quality of life measure developed by the EuroQol group. The EQ-5D-5L is self-administered and measures health 5 dimensions (mobility, self-care, usual activities, pain or discomfort, and anxiety or depression) and uses a visual analogue score to measure health today on a scale from 0 to 100

### Medical Outcome Study Sleep Scale (MOS Sleep)

The MOS Sleep is a sleep measure developed as part of the Medical Outcome Study (MOS). The questionnaire is self-administered and assesses 12 items; sleep disturbance, sleep adequacy, somnolence, quantity of sleep, snoring, and awakening short of breath or with a headache.

### Hospital Anxiety and Depression Score (HADS)

The HADS is a self-administered questionnaire comprising of seven questions for anxiety and seven questions for depression. Anxiety and depression scores are calculated independently and are categorised in the following thresholds: 8–10 mild, 11–14 moderate, 15–21 severe. For both scales, scores of less than 7 indicate non-cases.



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### Footplate Stimulation Programme and Parameters

6 7 8 9 10	Mode	Phase Duration (µs)	Basic Wave Frequency (kHz)	Frequency (Hz)	On Duration (s)	Off Duration (s)	Voltage (V) (Level=99)	Current (mA) (Level=99)	Voltage (V) (Level=50)	Current (mA) (Level=50)
11	Tolerance	±10%	±10%	±10%	±10%	±10%	±15%	±15%	±15%	±15%
12										
13	1	450	1.4	20.0	3.2	1.0	70	10.1	43	6.4
14	2	450	1.4	25.0	6.9	1.0	69	11.3	42	7.4
15	3	450	1.4	38.8	4.4	1.0	66	12.9	41	8.2
16	4	450	1.4	35.7	7.1	1.0	67	12.8	41	8.1
17	5	450	1.4	32.5	4.4	1.5	67	12.7	40	7.9
18	6	450	1.4	32.4	4.6	1.0	67	12.6	40	7.9
19	7	970	1.0	35.6	1.9	1.5	52	14.0	34	9.7
20	8	450	1.4	25.3	4.3	1.5	70	11.4	43	7.4
21	9	450	1.4	32.5	7.8	1.0	68	12.5	40	7.7
22	10	450	1.4	43.7	8.3	1.0	63	13.6	37	8.3
23	11	450	1.4	31.3	2.2	1.5	68	12.4	40	7.7
24	12	450	1.4	43.6	5.5	1.0	63	13.4	37	7.9
25	13	450	1.4	43.7	4.6	1.0	67	12.6	40	7.9
26	14	450	1.4	37.6	4.2	1.0	66	13.2	41	8.3
27	15	450	1.4	43.7	5.0	1.0	62	13.5	37	8.3
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8 **Quadriceps Stimulation Programme and Parameters**  
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Mode	Phase Duration ( $\mu$ s)	Basic Wave Frequency (kHz)	Frequency (Hz)	On Duration (s)	Off Duration (s)	Voltage (V) (Level=99)	Current (mA) (Level=99)	Voltage (V) (Level=50)	Current (mA) (Level=50)
Tolerance	$\pm 10\%$	$\pm 10\%$	$\pm 10\%$	$\pm 10\%$	$\pm 10\%$	$\pm 15\%$	$\pm 15\%$	$\pm 15\%$	$\pm 15\%$
1	450	1.4	32.5	33	27	65.2	12.2	41.2	8.14
2	450	1.4	32.5	13	17	65.2	12.2	41.2	8.14



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	Addressed on page number
<b>Administrative information</b>			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	___ 1 ___
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	___ 3-4 ___
	2b	All items from the World Health Organization Trial Registration Data Set	___ Complete ___
Protocol version	3	Date and version identifier	___ 2 ___
Funding	4	Sources and types of financial, material, and other support	___ 21 ___
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	___ 1 ___
	5b	Name and contact information for the trial sponsor	___ 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	___ 20 ___
	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)	___ 20 ___

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1	<b>Introduction</b>			
2				
3	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	___ 5-8 ___
4				
5				
6		6b	Explanation for choice of comparators	___ 5-8 ___
7				
8	Objectives	7	Specific objectives or hypotheses	___ 7-8 ___
9				
10	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)	___ 8 ___
11				
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14	<b>Methods: Participants, interventions, and outcomes</b>			
15				
16	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	___ 8 ___
17				
18				
19	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)	___ 9-10 ___
20				
21				
22	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	___ 11-13 ___
23				
24		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)	___ 13 ___
25				
26		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	___ 13 ___
27				
28		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	___ 10 ___
29				
30	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	___ 14-16 ___
31				
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34	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 ___
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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	8-9
2				
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4	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	9
5				
6	<b>Methods: Assignment of interventions (for controlled trials)</b>			
7	<b>Allocation:</b>			
8				
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10	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	11
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16	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	11
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20	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	11
21				
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24	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	11
25				
26				
27		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	11
28				
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31	<b>Methods: Data collection, management, and analysis</b>			
32				
33	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	14-16
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39		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	12
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1	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	_____18_____
2				
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5	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	_____18-19_____
6				
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8		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	_____18-19_____
9				
10		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)	_____18-19_____
11				
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13				
14	<b>Methods: Monitoring</b>			
15				
16	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	_____20_____
17				
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22		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	_____8_____
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25	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	_____11_____
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28	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	_____20_____
29				
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32	<b>Ethics and dissemination</b>			
33				
34	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	_____19_____
35				
36				
37	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)	_____20_____
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1	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	_____ 3 _____
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3				
4		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	_____ N/A _____
5				
6				
7	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	_____ 18, 20 _____
8				
9				
10	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	_____ 19-20 _____
11				
12				
13	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	_____ 20 _____
14				
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16	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	_____ 11 _____
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19				
20	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	_____ 3, 11, 19 _____
21				
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23				
24		31b	Authorship eligibility guidelines and any intended use of professional writers	_____ N/A _____
25				
26		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	_____ N/A _____
27				
28				
29	<b>Appendices</b>			
30				
31	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	_____ Attached _____
32				
33				
34	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	_____ N/A _____
35				
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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.

## Correction: *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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Briggs-Price S, Houchen-Wolloff L, Daynes E, *et al.* 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. *BMJ Open* 2022;12:e061113. doi: 10.1136/bmjopen-2022-061113

In above mentioned article, due to the commercial sensitivity of the device stimulation parameters they have been removed from the supplemental material. The main text in the article have been updated in section “Intervention.” The consent form was missing from the supplementary material and has now also been added.

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