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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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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

outcome. Participant focus groups will be completed following recruitment of half of the participants and after all participants have been recruited. Focus groups will be analysed via thematic analysis.

Ethics and Dissemination

Ethical approval has been obtained from the North-West Preston ethics committee and the trial has been registered through the ISRCTN registry (ISRCTN12112819). The study results will be disseminated to the appropriate stakeholders through presentations, conferences and peer-reviewed journals. Results will be presented to participants following study completion at the Biomedical Research Centre – Respiratory, Glenfield Hospital, Leicester.

ARTICLE SUMMARY *(*Strengths and limitations of this study)

- This study protocol describes a double-blind, randomised, sham-controlled trial investigating neuromuscular electrical stimulation (NMES) for individuals with osteoarthritis of the knee
- This protocol includes a powered (80%) sub group analysis for compliance to the active device
- The protocol includes focus groups to understand the participant experience of using NMES for osteoarthritis of the knee
- Limitation: compliance is measured through self-reported diaries and is not an embedded function of the device

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

of exercise interventions decreases over time [9]. Therefore finding an accessible modality that targets both pain and the muscular deficits seen in KOA is desirable.

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

Due to the current quality of evidence the clinical validity of NMES for symptomatic KOA remains unclear [23]. Previous trials exploring the effect of NMES for KOA have utilised a wide range of stimulation parameters and training frequencies [19]. In addition, previous research frequently combines NMES with exercise or other modalities; therefore it is difficult to determine the unique impact of NMES from a multifaceted intervention. This has caused significant variability in results with regards to quadriceps strengthening and associated pain relief. Challenges for NMES prescription include individualising the stimulation intensity to individual tolerance whilst aiming to achieve sufficient stimulation to produce physiological adaptations. Progression of NMES intensity is important during an

NMES programme as individuals become habituated to the sensation. Progressing intensity recruits additional muscle fibres at a greater distance from the electrode site increasing the potential area for muscular adaptation [24].

NMES investigations frequently include targeting isolated muscle groups in the treatment of KOA [20-22, 25]. Muscle deficits are most frequently reported in the knee extensors compared to the surrounding muscle groups in KOA, although strength deficits are seen throughout the lower limb [26]. Compared to healthy controls, individuals with KOA present with weakness and altered activation patterns in the plantarflexors [27-29]. Both the knee extensors and plantarflexors are important muscle groups involved in propulsion during the gait cycle. Walking speed is a predictor of function and mortality in older adults and slower walking speed is associated with KOA [30]. NMES has been shown to be an effective intervention for increasing strength in the plantarflexors in healthy populations [31]. To the authors knowledge there have been no previous investigations into calf and foot NMES in the KOA population. It is unknown if stimulating several muscle groups around the knee will provide superior pain relief and functional performance for individuals with KOA.

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

The objectives for the trial are: 1) to determine the effects of a NMES device on pain, strength, swelling, health related quality of life, sleep, anxiety, depression, exercise capacity and physical activity in participants with symptomatic KOA when compared with a sham device; 2) to conduct a subgroup analysis (per protocol) based on compliance, self-administered stimulation intensity, baseline pain and function and knee extensor strength to explore if there is a subgroup of patients who receive the most benefit from NMES 3) to conduct focus groups to explore participant experiences of using a NMES device for the management of KOA.

METHODS AND ANALYSIS

Trial Design and Registration

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

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). 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 preprogramed 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.

The quadriceps stimulation consists of two 10x12.5cm self-adhesive electrodes for unilateral stimulation (Figure. 3). The quadriceps electrodes are placed proximally to rectus femoris motor point and distally covering the vastus medialis motor point [36]. The quadriceps electrodes provide two patterns of stimulation allowing users to familiarise with the sensation before entering into a second phase of the strengthening protocol. The quadriceps stimulation programme lasts 20 minutes and is detailed in the supplementary material. Participants are instructed to use the 20 minute quadriceps stimulation programme 5 times per week.

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

The sham device footplate and stimulation pads appear indistinguishable from the active device. The sham device is operationally identical including remote activation and control. The sham device voltage and current is limited to ensure no muscular contraction. When demonstrating the sham device the unblinded researcher will inform the participant that it

is expected and normal to not experience a sensation. Participants will have no prior experience of using NMES and will therefore be unable to distinguish between active and sham devices.

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

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

Outcome Measures

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

Primary Outcome – 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

Scale (MOS Sleep) [41] and Hospital Anxiety and Depression Score (HADS) [42]. Details of each measure are provided in the supplementary material.

Exercise Capacity

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

Knee Extensor Strength

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

Swelling

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

intensity level achieved. There will also be a section provided for participants to record any changes in pain medication, activity levels, health status or other health care interventions.

Qualitative Focus Groups

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

Data analysis plan

Data collected will be entered into a secure online database 'Research Electronic Data Capture' (REDCap) [46. 47] by authorised members of the researcher team. Baseline characteristics will be described and group comparison will be analysed using an independent t-test or non-parametric test. An intention to treat analysis will be completed. Changes in all outcomes will be described pre and post intervention and analysed using paired t-test's or non-parametric equivalent, the primary outcome being the WOMAC pain

domain at 8 weeks. Differences between time points and groups will be compared using repeated measures ANOVA. Baseline scores will be included as covariates within the ANOVA analysis to account for any significant differences. The WOMAC questionnaire will also be compared between groups at the 16 week time point. An analysis of 'responders' and 'non-responders' will be explored for all outcomes following data collection. Responders are defined as participants who achieve a 20% improvement in the primary outcome during the 8-week intervention phase.

Pre-defined subgroup analyses will be performed on: 1) compliant versus non-compliant (compliance defined within compliance section above) a per protocol analysis, 2) participants who were able to attend the study site prior to and following COVID-19 study site attendance restrictions 3) recruitment source (e.g orthopaedic clinics, physiotherapy clinics, GP Registers). Further exploratory analyses will be performed on physical activity measures.

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

ETHICS AND DISSEMINATION

Ethical approval was provided by the North-West Preston Research Ethics Committee on the 22nd February 2017. Findings from the trial will indicate the clinical effectiveness of this NMES device. The findings of this trial are expected to be published and publically available

within 2022. These findings will be disseminated in line with the Centre for Exercise and Rehabilitation Science dissemination strategy. Dissemination will be completed to participants of the trial and more broadly to health care professionals, patients, members of the public and academics. The results of the study will be presented at regional and national musculoskeletal conferences.

AUTHORS' CONTRIBUTIONS

All authors co-developed the protocol. The manuscript was prepared by S.Briggs-Price and approved by all authors.

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COMPETING INTERESTS STATEMENT

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

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Figure Legends

Figure.1 Flow diagram of study procedures

Figure.2 NMES Device Footplate

Figure.3 NMES Quadriceps Electrodes

Figure 1. Flow diagram of study procedures

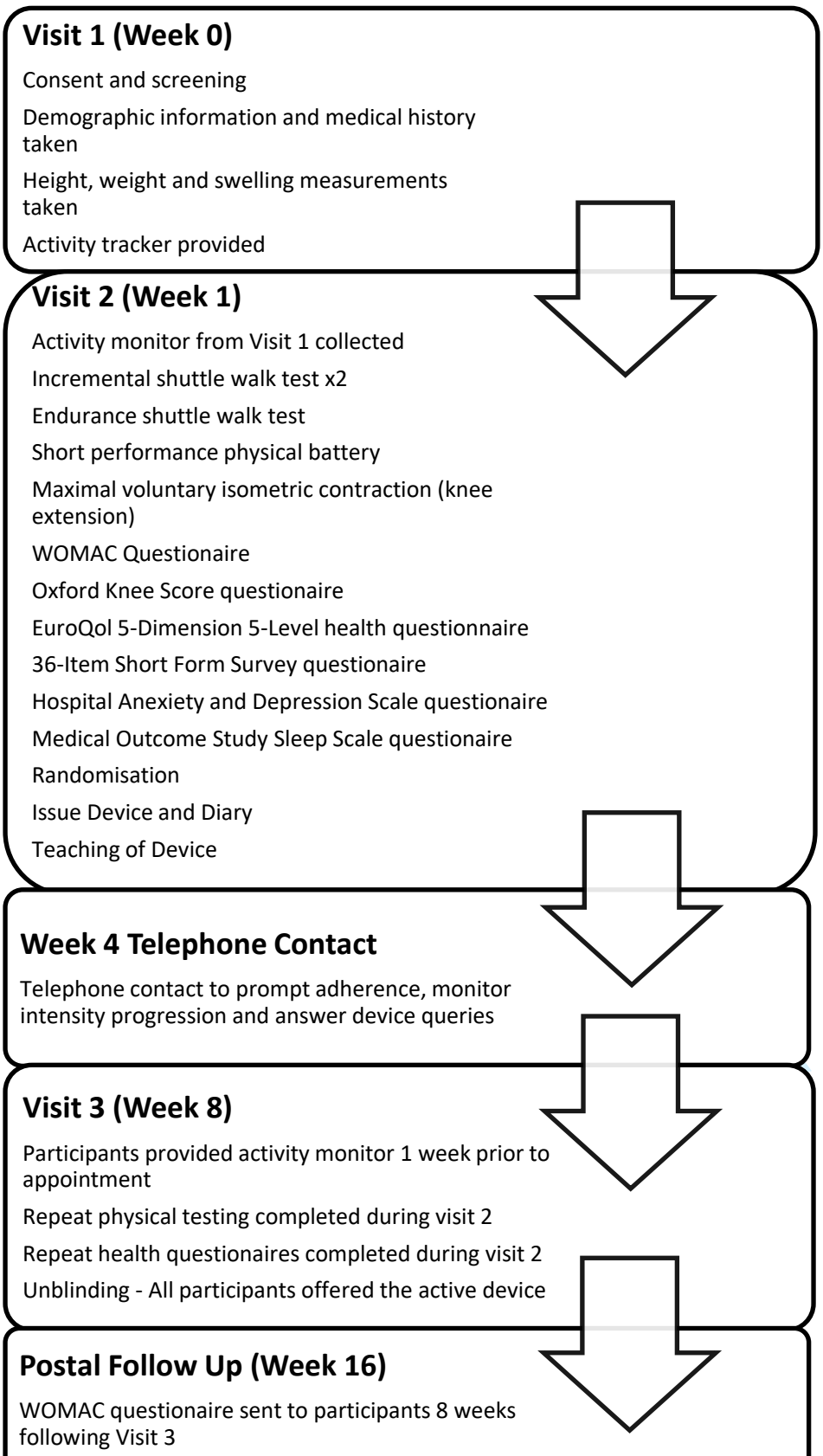

Figure.2 NMES Device Footplate

159x158mm (72 x 72 DPI)

Figure.3 NMES Quadriceps Electrodes

264x148mm (96 x 96 DPI)

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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Manuscript ID	bmjopen-2022-061113.R1
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Primary Subject Heading:	Rehabilitation medicine
Secondary Subject Heading:	Rehabilitation medicine
Keywords:	Knee < ORTHOPAEDIC & TRAUMA SURGERY, Rehabilitation medicine < INTERNAL MEDICINE, Musculoskeletal disorders < ORTHOPAEDIC & TRAUMA SURGERY

Note: The following files were submitted by the author for peer review, but cannot be converted to PDF. You must view these files (e.g. movies) online.
Main Text.docx

Figure 1. Flow diagram of study procedures

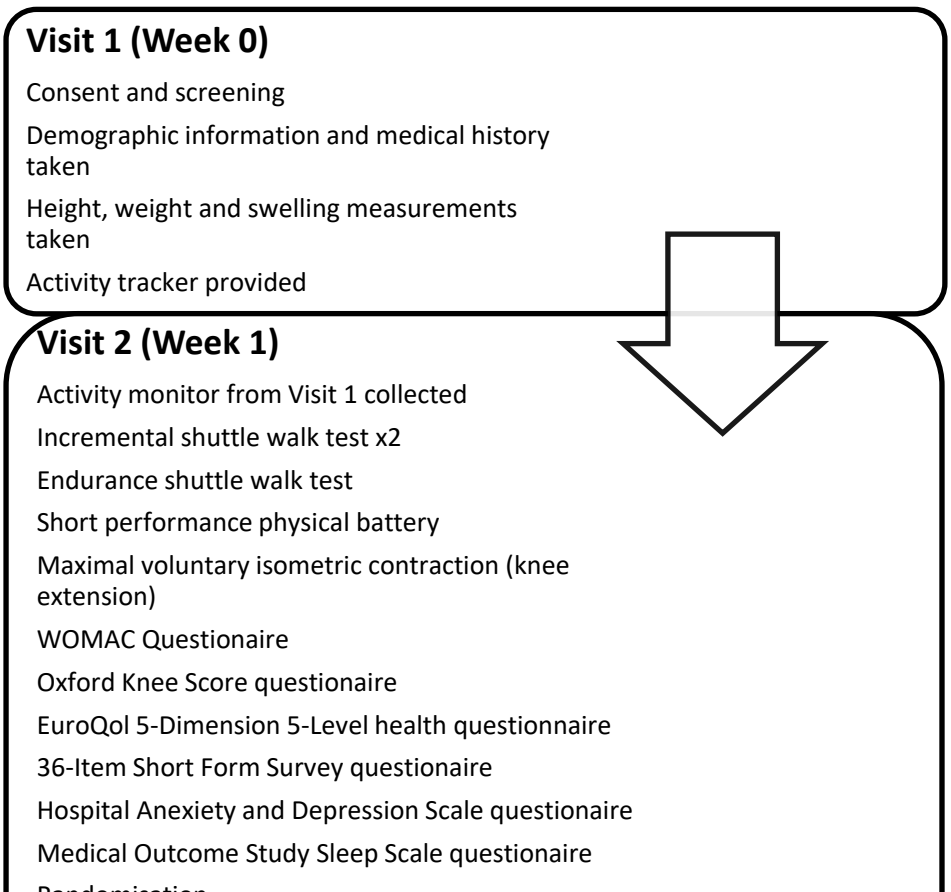

Figure.2 NMES Device Footplate

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.

Footplate Stimulation Programme and Parameters

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

Quadriceps Stimulation Programme and Parameters

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	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

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

Section/item	Item No	Description	Addressed on page number
Administrative information			
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_____

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5-8
	6b	Explanation for choice of comparators	5-8
Objectives	7	Specific objectives or hypotheses	7-8
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
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	9-10
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	11-13
	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
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	13
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	10
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
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 1

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	___8-9_____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	____9_____
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	____11_____
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_____
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	____11_____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	____11_____
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	____11_____
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	____14-16_____
	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_____

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
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
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	18-19
	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
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	20
	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
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
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	20
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	19
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

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	_____3____
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	____N/A_____
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_____
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	_____19-20___
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_____
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_____
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____
	31b	Authorship eligibility guidelines and any intended use of professional writers	_____N/A_____
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	___N/A_____
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	__Attached__
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_____

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

BMJ Open

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

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Primary Subject Heading:	Rehabilitation medicine
Secondary Subject Heading:	Rehabilitation medicine
Keywords:	Knee < ORTHOPAEDIC & TRAUMA SURGERY, Rehabilitation medicine < INTERNAL MEDICINE, Musculoskeletal disorders < ORTHOPAEDIC & TRAUMA SURGERY

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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Word Count: 3310

Keywords: Knee, Osteoarthritis, Electrical Stimulation

ABSTRACT

Introduction

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

Methods and analysis

193 individuals with KOA will be recruited to a single-centre, double-blind, randomised, sham-controlled trial at the Respiratory Biomedical Research Centre, Leicester, United Kingdom. Participant will be randomised (1:1) to follow an 8-week home-based intervention using a NMES device or sham device. The NMES device consists of footplate electrodes and two quadriceps electrodes. Footplate stimulation will be completed daily for 30 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 subgroup analysis for compliance to the active device will be

complete for the primary outcome. Participant focus groups will be completed following recruitment of half of the participants and after all participants have been recruited.

Ethics and dissemination

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

Trial registration number

ISRCTN registry, ISRCTN12112819 (date registered 01/05/2019). IRAS registry 219693. University Hospitals of Leicester registry 91017. Protocol Version 8.

Strengths and limitations of this study

- This study protocol describes a double-blind, randomised, sham-controlled trial investigating neuromuscular electrical stimulation (NMES) for individuals with osteoarthritis of the knee.
- This protocol includes a powered (80%) subgroup analysis for compliance to the active device.

- The protocol includes focus groups to understand the participant experience of using NMES for osteoarthritis of the knee.
- One limitation of the study is that compliance is measured through self-reported diaries and is not an embedded function of the device.

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

of exercise interventions decreases over time [9]. Therefore finding an accessible modality that targets both pain and the muscular deficits seen in KOA is desirable.

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

Due to the current quality of evidence the clinical validity of isolated NMES of the quadriceps for symptomatic KOA remains unclear [23]. Previous trials exploring the effect of NMES for KOA have utilised a wide range of stimulation parameters and training frequencies [19]. In addition, previous research frequently combines NMES with exercise or other modalities; therefore it is difficult to determine the unique impact of NMES from a multifaceted intervention. This has caused significant variability in results with regards to quadriceps strengthening and associated pain relief. Challenges for NMES prescription include individualising the stimulation intensity to individual tolerance whilst aiming to achieve sufficient stimulation to produce physiological adaptations. Progression of NMES

intensity is important during an NMES programme as individuals become habituated to the sensation. Progressing intensity recruits additional muscle fibres at a greater distance from the electrode site increasing the potential area for muscular adaptation [24].

NMES investigations frequently include targeting isolated muscle groups in the treatment of KOA [20-22, 25]. Muscle deficits are most frequently reported in the knee extensors compared to the surrounding muscle groups in KOA, although strength deficits are seen throughout the lower limb [26]. Compared to healthy controls, individuals with KOA present with weakness and altered activation patterns in the plantarflexors [27-29]. Both the knee extensors and plantarflexors are important muscle groups involved in propulsion during the gait cycle. Walking speed is a predictor of function and mortality in older adults and slower walking speed is associated with KOA [30]. NMES has been shown to be an effective intervention for increasing strength in the plantarflexors in healthy populations [31]. To the authors knowledge there have been no previous investigations into calf and foot NMES in the KOA population. It is unknown if stimulating several muscle groups around the knee will provide superior pain relief and functional performance for individuals with KOA.

An NMES device (Revitive Arthritis Knee®) has been developed to improve lower limb strength, function, swelling and pain in individuals with KOA. Unlike previous NMES devices, the device provides stimulation to the musculature of the knee both proximally and distally. The device consists of electrodes for quadriceps stimulation and footplate electrodes for stimulation of the calf and foot. The footplate has previously been investigated for its influence on peripheral artery disease and chronic venous disease and was found to significantly improve circulation and walking distance [32, 33]. These investigations did not

include quadriceps stimulation and there have been no investigations into the effects of the device for KOA.

The objectives for the trial are: 1) to determine the effects of a NMES device on pain, strength, swelling, health related quality of life, sleep, anxiety, depression, exercise capacity and physical activity in participants with symptomatic KOA when compared with a sham device; 2) to conduct a subgroup analysis (per protocol) based on compliance, self-administered stimulation intensity, baseline pain and function and knee extensor strength to explore if there is a subgroup of patients who receive the most benefit from NMES 3) to conduct focus groups to explore participant experiences of using a NMES device for the management of KOA. The trial hypothesis is an expected 20% difference in the primary outcome (WOMAC pain) at 8 weeks between groups in favour of the active device.

METHODS AND ANALYSIS

Trial design and registration

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

Participants

The sample size was calculated to detect a 20% difference (SD=19) between groups using a significance level of 0.05 for the WOMAC pain domain with 90% power. This requires 62 participants to complete the protocol (n=31 in each group). An expected drop-out rate of 30% was predicted, requiring 80 participants in total. In addition, the required recruitment to provide statistical power for the WOMAC pain domain for compliant participants in the active arm was prospectively calculated. Compliance is defined as completing 20 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 128 participants would be required to be recruited in each arm to allow a powered subgroup analysis for a compliant group within the active arm.

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

Participants will be recruited from outpatient physiotherapy clinics, orthopaedic 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 National Institute for Health and Care Excellence (NICE) guidelines [35]

  NICE diagnostic criteria: individual is 45 or over, has activity-related joint pain and has either no morning joint-related stiffness or morning stiffness that lasts no longer than 30 minutes; KOA is diagnosed clinically without requiring radiographic investigations
- Aged 45-85 years

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

- Fitted with an electronic implant such as a pacemaker or defibrillator
- Pregnant
- Existing or undergoing treatment for a 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 osteoarthritis of the hip, ankle or foot effecting mobility more than the effected knee
- Current or recent knee surgery or injury in the last 3 months
- Had a total knee replacement, partial knee replacement or high tibial osteotomy on the knee to be studied
- Had a corticosteroid or hyaluronic acid injections in the last 6 months
- BMI over or equal to 40
- Completing a concomitant physiotherapy programme

- Current use of transcutaneous electrical nerve stimulation (TENS)
- Current or previous use of neuromuscular stimulation device
- Unable to mobilise
- Inability to provide informed consent

Randomisation

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

Patient and public involvement

When developing the trial protocol, a patient and public involvement (PPI) meeting was conducted to discuss the feasibility of the intervention and trial visits. Advice from PPI members provided guidance on explaining participant randomisation, administering the device and the format of the participant diaries. Following completion of the trial, participants will be offered the opportunity to attend study steering committee meetings.

They will have the opportunity to provide feedback on the trial and guide trial management. Following data analysis, participants will be invited to a dissemination event at the Biomedical Research Centre – Respiratory, Glenfield Hospital, Leicester.

Intervention

The NMES device footplate (Figure. 2) provides a 30 minute programme of pulsed current with 15 different preprogramed 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.

The quadriceps stimulation consists of two 10x12.5cm self-adhesive electrodes for unilateral stimulation (Figure. 3). The quadriceps electrodes are placed proximally to rectus femoris motor point and distally covering the vastus medialis motor point [36]. The quadriceps electrodes provide two patterns of stimulation allowing users to familiarise with the sensation before entering into a second phase of the strengthening protocol. The quadriceps stimulation programme lasts 20 minutes and is detailed in the supplementary

material. Participants are instructed to use the 20-minute quadriceps stimulation programme 5 times per week.

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

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

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

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

Outcome measures

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

Primary outcome – 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 Scale (MOS Sleep) [41] and Hospital Anxiety and Depression Score (HADS) [42]. Details of each measure are provided in the supplementary material.

Exercise capacity

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

Knee extensor strength

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

Swelling

Swelling of the knee and ankle will be assessed through joint line circumference measurements of the knee and ankle at week 0 and week 8 using a flexible tape measure. Three measurements will be taken and the mean calculated. Measurements will be taken prior to randomisation and repeated by a blinded assessor on visit 3. Circumference measurements of the knee have been shown to achieve high levels of inter-relater 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 for both groups will be recorded in a self–reported participant diary provided at visit 2. The diary will record the date of use, time of use, stimulation location ('thigh pads' or 'footplate'), duration of use and peak intensity level achieved. There will also be a section provided for participants to record any changes in pain medication, activity levels, health status or other health care interventions.

Qualitative focus groups

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

Data analysis plan

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

Pre-defined subgroup analyses will be performed on: 1) compliant versus non-compliant (compliance defined within compliance section above) a per protocol analysis, 2) participants who were able to attend the study site prior to and following COVID-19 study site attendance restrictions 3) recruitment source (e.g orthopaedic clinics, physiotherapy clinics, GP Registers). Further exploratory analyses will be performed on physical activity measures.

Qualitative focus groups will be transcribed verbatim and analysed through NVivo version 12 (QSR International) using thematic analysis [48]. The main themes generated from the

analysis will be discussed with participants of the focus groups to ensure the discussion was represented accurately.

ETHICS AND DISSEMINATION

Ethical approval was provided by the North-West Preston Research Ethics Committee on the 22nd February 2017 (17/NW/0081). Participants provided informed consent following review of the participant information sheet and discussion regarding study procedures with a member of the research team. Findings from the trial will indicate the clinical effectiveness of this NMES device. Conduct of the trial began on 13/05/2019 and the data collection will be completed within 2022. These findings will be disseminated in line with the Centre for Exercise and Rehabilitation Science dissemination strategy and will be submitted for publication in a peer-reviewed journal.

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

COMPOSITION, ROLES, AND RESPONSIBILITIES

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

completion of all data collection. Trial analysis will be completed by the research team within University Hospitals of Leicester or an independent statistician.

PROTOCOL MODIFICATIONS

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

PRIMARY TRIAL SPONSOR

Actegy Ltd (Bracknell, UK).

CONTRIBUTORS

SS is the principal investigator of the research trial. SS, SBP, LHW, ED, LL, CE were involved in the development of the intervention and design of the trial. SS, SBP, LHW, ED , LL, CE, CG, GM have been involved in drafting the work or revising it critically for important intellectual content and have given the final approval of the version published.

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COMPETING INTERESTS

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

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D. Targett reviewed the sample size calculations.

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Figure titles

Figure 1. Flow diagram of study procedures

Figure 2. NMES Device Footplate

Figure 3. NMES Quadriceps Electrodes

Figure 1. Flow diagram of study procedures

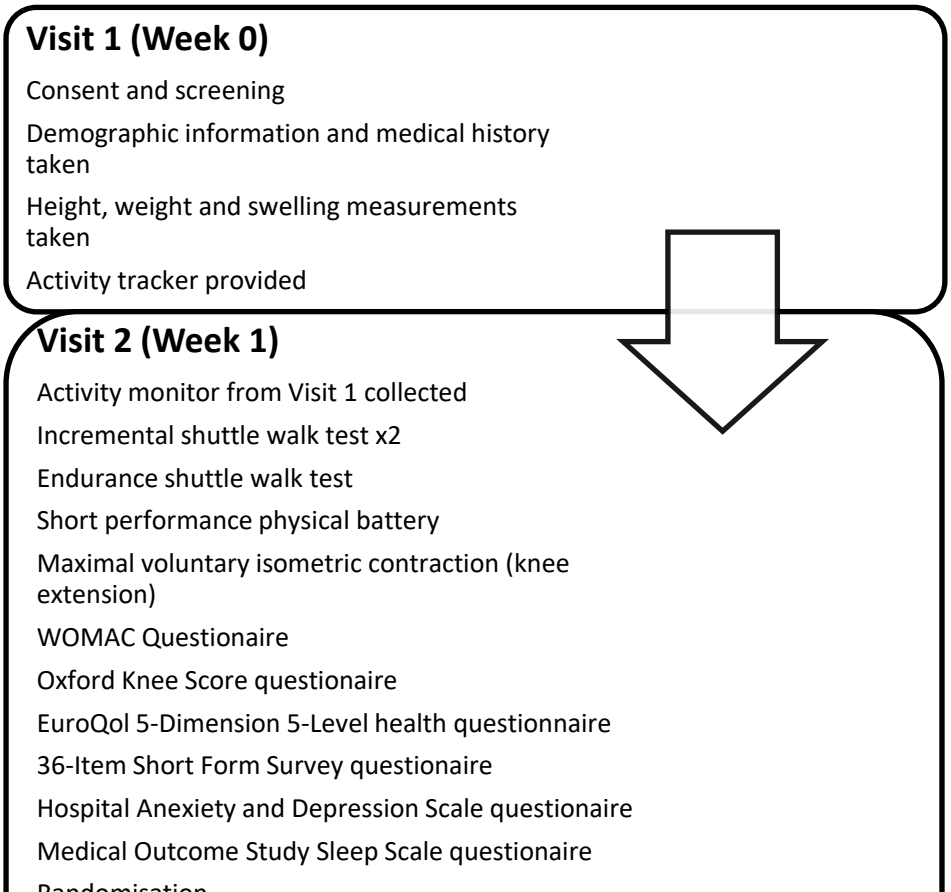

Figure.2 NMES Device Footplate

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.

Footplate Stimulation Programme and Parameters

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

Quadriceps Stimulation Programme and Parameters

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	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

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

Section/item	Item No	Description	Addressed on page number
Administrative information			
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_____

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5-8
	6b	Explanation for choice of comparators	5-8
Objectives	7	Specific objectives or hypotheses	7-8
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
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	9-10
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	11-13
	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
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	13
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	10
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
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 1

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	___8-9_____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	____9_____
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	____11_____
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_____
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	____11_____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	____11_____
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	____11_____
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	____14-16_____
	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_____

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
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
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	18-19
	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
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	20
	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
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
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	20
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	19
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

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	_____3____
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	____N/A_____
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_____
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	_____19-20___
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_____
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_____
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____
	31b	Authorship eligibility guidelines and any intended use of professional writers	_____N/A_____
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	___N/A_____
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	__Attached__
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_____

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

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*

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.

BMJ Open 2022;**12**:e061113corr1. doi:10.1136/bmjopen-2022-061113corr1