

Chapter 8. Six-weeks of home-based NMES improves knee extensor endurance and function in healthy, older adults – A feasibility study.

8.1 Chapter introduction

Chapter 8 of this thesis describes the final research study, where an NMES intervention, designed to improve knee extensor endurance, was tested in a cohort of healthy, older adults, as an accumulation of this research to date. It was originally planned to test this intervention amongst a clinical population, however due to the suspension of elective joint replacement surgeries, and the limitations to research in healthcare settings due to Covid-19 described in sections 6.3 and 6.4.4, the decision was made to test the intervention in a non-clinical population instead. The planned research would have been novel in that few studies have evaluated the effects of NMES in patients undergoing hip replacement, and to date, no study has examined an NMES intervention targeting at improving knee extensor endurance in a hip osteoarthritis population (Burgess et al. 2019). Nonetheless, it was possible to evaluate a novel NMES protocol in a healthy, aged-matched cohort, and this research provides important findings that will be used to develop NMES interventions in clinical populations in the future. Furthermore, to date, research evaluating the strengthening benefits of NMES in healthy older adults is sparse (Langeard et al. 2017; Rahmati et al. 2021), and little work has been conducted to examine how endurance capacity can be improved in this population. Therefore, this research is novel and contributes to the evidence-base within the general older adult population, as well as underpinning future investigations in orthopaedic populations.

8.2 Rationale

To date, this research has drawn the following conclusions:

1. The incidence of hip osteoarthritis and hip replacement surgeries is increasing (National Joint Registry 2021), and many patients do not return to their pre-surgery level of function or physical activity in the weeks or years following surgery (Smith et al. 2017; Smith et al. 2018).
2. Current rehabilitation practice in hip replacement may be ineffective in producing a level of neuromuscular activation required to induce a muscle strength adaption before and after surgery (Gavin et al. 2018) and therefore may have limited effect on patient function or quality of life in the weeks or months following surgery (Smith et al. 2008; Smith et al. 2009). In addition, older adult and osteoarthritic populations may be reluctant to participate in voluntary resistance training due to pain, discomfort, or external barriers such as cost and travel requirements (Burton et al. 2017). Therefore, innovative rehabilitation methods are required to address muscle weakness.

3. There is increasing evidence to suggest NMES can improve strength in patient populations, including emerging evidence from knee osteoarthritis and knee replacement populations (Chapter 3), and anecdotal evidence for its effectiveness in patients who have had hip replacement surgery (Burgess et al. 2019).
4. Individuals with moderate-to-severe hip osteoarthritis demonstrate significant weakness of the knee extensors, knee flexors and hip abductors when compared to their healthy counterparts (Chapter 4) (Burgess et al. 2021c).
5. Knee extensor endurance may be the most considerably impaired measure, and the impact of this has been demonstrated by the findings of a functional assessment, whereby people with hip osteoarthritis take considerably longer to complete tasks such as walking, stair climbing, and rising from a chair (Chapter 4) (Burgess et al. 2021c). Functional ability is paramount to maintain mobility and independence in older adult and musculoskeletal populations, and therefore innovations are required to improve this measure.
6. NMES of the knee extensors is tolerable and may be a feasible treatment method to address muscle weakness in the hip osteoarthritis population (Chapter 5) (Burgess et al. 2021b). However, it is unlikely that NMES of the hip abductors can be applied at an intensity sufficient to evoke muscle hypertrophy and subsequent strength gains due to adipose tissues surrounding the gluteus medius, gluteus minimus and tensor fascia latae (Burgess et al. 2021b).
7. When prescribing NMES, providing clear instructions, an NMES training programme, comprehensive instructions and a familiarisation period may help to increase adherence and fidelity to the protocol (Chapter 7) (Burgess et al. 2021a). In addition, setting intensity thresholds based upon patient tolerance, using built-in adherence trackers and participant diaries, marking electrode placement and monitoring pain levels during stimulation may help to increase compliance (Burgess et al. 2021a).

Study aim

The research accumulated in this thesis was used to inform the design of the final study, described in section 8.3, whereby an NMES intervention was designed and tested amongst a cohort of healthy, older adults. The aim of this study was to determine the feasibility of NMES for increasing knee extensor endurance, and subsequent functional performance, in healthy older adults, with the aim of informing future work in patients with hip osteoarthritis undergoing joint replacement surgery.

Objectives

1. Assess recruitment, retention, and adherence rates to a six-week intervention of home-based NMES in an older adult population.

2. Determine acceptability and usability of a six-week intervention of home-based NMES to an older adult population.
3. Explore whether six weeks of home-based NMES leads to improvements in muscle endurance and maximal muscle strength.
4. Explore whether improvements in muscle endurance and maximal muscle strength translate to improvements in mobility and function.

8.3 Methodology

Trial design

This study was a single centre feasibility trial, recruiting 12 adults with no significant neurological or musculoskeletal disorders from the local community in Bournemouth, UK between 9th May 2022 and 2nd September 2022. The experimental protocol was approved by the Bournemouth University ethics committee on 4th April 2022 (Appendix 9). In keeping with good practice, this study was conducted according to ISO 14155:2011 Clinical investigation of medical devices for human subjects — Good Clinical Practice, applicable government regulations and all relevant policies and procedures and with the ethical principles that have their origin in the Declaration of Helsinki 1996 (World Medical Association 2018). The CONSORT 2010 statement: extension to randomised pilot and feasibility trials was used to guide the reporting of this study (Eldridge et al. 2016), with consideration of the recommendations for use in non-randomised trials (Lancaster and Thabane 2019).

Participants

Participants were recruited from the local area through online advertisement (Facebook, Twitter) and email recruitment sent to local organisations, such as the University of the 3rd Age. Those interested in the study contacted the researcher for an informal discussion and were subsequently screened via a telephone call to ensure they met the eligibility criteria. Suitable participants were invited to attend a baseline assessment at Bournemouth University, where they were screened for Covid-19, their eligibility was confirmed, and their informed consent received. Following the consent process, participants took part in an NMES training session. In this session, participants were shown the device and how to operate it, and their physiological response to NMES was tested, to ensure an involuntary muscle contraction could be achieved by the device. Once participants could demonstrate independent use of the device, they participated in six weeks of home-based NMES training. Participants were contacted every two weeks by telephone, so they were able to report any adverse events or device deficiencies and have their NMES dose reviewed. Participants were invited to return to the University seven weeks from their baseline appointment, where their baseline measures were repeated, and they were asked to provide their feedback on the usability of the device. The study flowchart is presented in Figure 15.

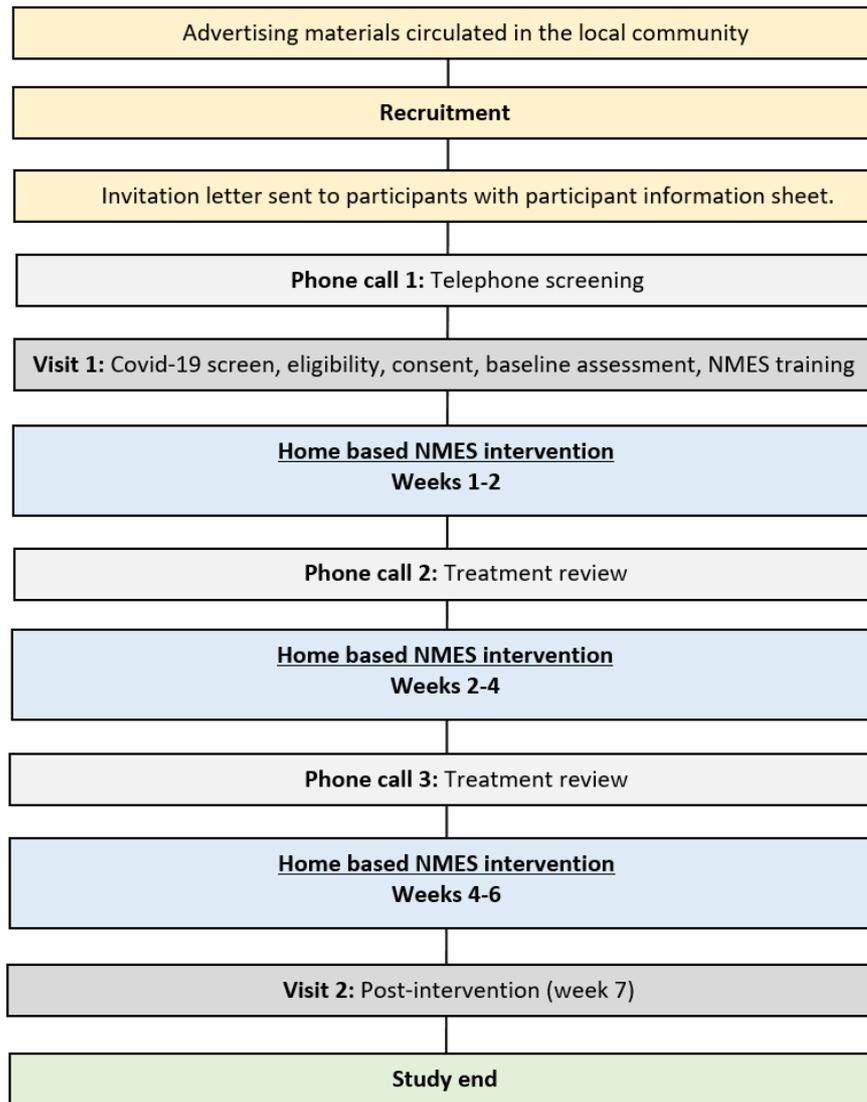


Figure 15. Study flowchart

Own image

Eligibility criteria

Participants were included if they were aged 60 years or older, were not receiving an active medical treatment for a neurological or musculoskeletal disorder and met the predetermined eligibility criteria listed in Table 4.

Inclusion	Exclusion
<ul style="list-style-type: none"> • 60 years or older • Healthy with no significant neurological or musculoskeletal disorders • Able to complete study intervention and post-intervention assessment • Passed the ‘response to NMES’ test to ensure the NMES could produce an involuntary muscle contraction 	<ul style="list-style-type: none"> • Under 60 years • Receiving an active medical treatment for a neurological or musculoskeletal disorder • Had a neurological disease affecting their walking ability • Fitted with a pacemaker or other active medical implant • Suffered from uncontrolled epilepsy • Had sepsis or osteomyelitis • Had a poor skin condition that would prevent the use of electrodes • Not physically able to use the Primus muscle testing equipment or complete the functional tests • Participating in any form of muscle strengthening programme aimed at improving the quadricep muscles strength • Not able to provide informed consent

Table 4. Eligibility criteria for inclusion in the study

Intervention

Consistent with the previous stages of this research, the NMES device chosen for this study was the Orthopaedic Microstim 2V2 neuromuscular stimulator (developed by Odstock Medical Ltd, Salisbury, UK). The device has been developed for general orthopaedic use, and for following joint replacement surgery, and consists of a stimulator box with two leads which are connected to two multiple use self-adhesive electrodes. The device is CE marked, and a commercially available device, pre-set with stimulation programmes designed to suit orthopaedic patients (for example, pain reduction, increasing blood flow, improving muscle endurance and muscle power), informed by a literature review of the available evidence.

All participants were trained how to use the NMES device by a Professor in Clinical Engineering with over 30 years of experience prescribing NMES. To proceed with the study, all participants were required to demonstrate safe and independent use of the device at the University before using it at home.

NMES was applied to the quadriceps femoris muscle group using two PALS platinum 70 mm (2.75”) round electrodes positioned on the rectus femoris (negative) and vastus medialis (positive), in line with manufacturer instructions and previous work described in Chapter 5. Electrode positioning was approximate to the placement show in Figure 16 and was tested during the training session to ensure a contraction could be achieved.

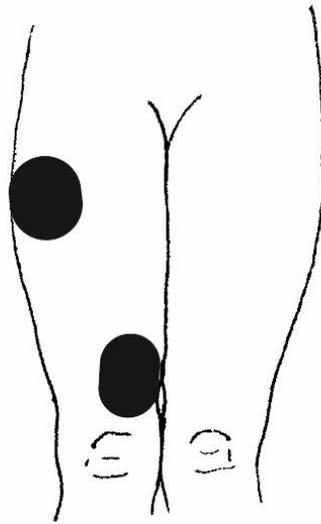


Figure 16. Approximate location of electrode positioning on the quadriceps

Used with permission of Odstock Medical Ltd

NMES dose

The device was pre-set with stimulation parameters targeted at increasing muscle endurance (Table 5). In knee osteoarthritis, published guidelines have suggested prescribing NMES at a frequency of between 50 – 75 Hz, with a pulse duration of between 200 μ s - 400 μ s and a treatment duration of 20 minutes in order to achieve maximal strength gains (Novak et al. 2020). However, while higher frequencies may generate a stronger muscle contraction, they can also rapidly increase the rate of muscle fatigue, causing users to set the stimulation intensity to a lower level than they would if using a lower frequency. Given that the current intensity determines the number of nerve fibres recruited, the resulting effect may be that a smaller number of muscle fibres being exercised with the suggested parameters. Therefore, the frequency was pre-set at 20 Hz, with 10 seconds on, 3 seconds off duty cycle, including a 0.5 second ramp up and down, and a 300 μ s pulse duration. This long “on” cycle was chosen to induce a change in muscle fibre properties from fast to slow, with the aim of improving fatigue resistant muscle fibres, in line with previous research identifying a diminished endurance capacity of the knee extensor muscle group in individuals with hip osteoarthritis (Chapter 4). Participants in this

study were asked to use the device twice a day, five days a week, with session duration increasing from 15 minutes to 30 minutes over the six-week course with the aim of improving knee extensor endurance.

Informed by findings from Chapter 7, stimulation current intensity thresholds were set based upon participant tolerance and monitored throughout the study to ensure a muscle contraction was achieved, without causing the participant pain. Participants were given targets to achieve in terms of the minimum muscle contraction achieved, described using the Medical Research Council's (MRC) scale for muscle power (Table 6). In addition, in line with recommendations to maximise spatial recruitment while using NMES (Maffiuletti 2010), participants were encouraged to increase stimulation intensity to the maximum they could tolerate to depolarise deeper nerve fibres, thereby causing a greater muscle contraction. The NMES dose was reviewed during biweekly phone calls from the lead researcher, so that it could be adjusted if necessary. In line with preliminary work described in Chapter 7, participants were provided with written instructions (Appendix 7), a programme training schedule (Table 4), a built-in adherence tracker and a participant diary (Appendix 8) to encourage adherence and fidelity to the intervention (Burgess et al. 2021a).

	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
Treatment duration	15 minutes	20 minutes	25 minutes	25 minutes	30 minutes	30 minutes
Sessions per day	2	2	2	2	2	2
Days per week	5	5	5	5	5	5
Positioning	Seated, with knees slightly flexed (approximately 20°)	Seated, with knees slightly flexed (approximately 20°)	Seated, with knees slightly flexed (approximately 20°)	Seated, with knees slightly flexed (approximately 20°)	Seated, with knees slightly flexed (approximately 20°)	Seated, with knees slightly flexed (approximately 20°)
Minimum current intensity	Sufficient to induce a visible quadriceps contraction (MRC 1)	Sufficient to induce visible quadriceps contraction (MRC 1)	Sufficient to induce isotonic quadriceps contraction (MRC 3)	Sufficient to induce isotonic quadriceps contraction (MRC 3)	Sufficient to induce isotonic quadriceps contraction (MRC 3)	Sufficient to induce isotonic quadriceps contraction (MRC 3)
Frequency	20 Hz	20 Hz	20 Hz	20 Hz	20 Hz	20 Hz
Duty Cycle	10 s on, 3 s off	10 s on, 3 s off	10 s on, 3 s off	10 s on, 3 s off	10 s on, 3 s off	10 s on, 3 s off
Ramp	0.5 sec	0.5 sec	0.5 sec	0.5 sec	0.5 sec	0.5 sec
Pulse duration	300 μs	300 μs	300 μs	300 μs	300 μs	300 μs
Stimulation format	Simultaneous	Simultaneous	Simultaneous	Simultaneous	Simultaneous	Simultaneous
Device setting	7	7	7	7	7	7

Phone call – Treatment review

Phone call – Treatment review

Table 5 NMES intervention

Score	Description
0	No muscle activation
1	Trace muscle activation, such as a twitch, without achieving full range of motion
2	Muscle activation without gravity resistance, achieving full range of motion
3	Muscle activation against gravity, full range of motion
4	Muscle activation against some resistance, full range of motion
5	Muscle activation against examiner's full resistance, full range of motion

Table 6 MRC scale of muscle power

Used with permission of the Medical Research Council

Outcomes

Age, weight, and height were recorded from all participants. Physical activity levels were collected using the Physical Activity Scale for the Elderly (PASE) questionnaire (Appendix 5) (Washburn et al. 1993). The outcome measures described below were collected at baseline, and then seven weeks later, to evaluate the effects of the NMES device on quadriceps strength, and the feasibility of the intervention.

Feasibility

Data on recruitment, retention and attrition were recorded as measures of feasibility (Bowen et al. 2009). In addition, device acceptability and adherence to the study protocol were collected to assess the feasibility of the intervention (Bowen et al. 2009). Device acceptability was measured using a questionnaire adapted from previous evaluations of acceptability of NMES (Appendix 12) (Burgess et al. 2021b). Questions were related to pain, discomfort, usability, and acceptability. Furthermore, the System Usability Scale (SUS) (Appendix 13) was used to evaluate the usability of the device (Brooke 1986). Adherence to the NMES intervention was recorded by a built-in adherence tracker that recorded total minutes used and times switched on, and a participant diary, that collected information on dates and duration of the NMES sessions, amplitude settings (in milliamps (mA) and level of discomfort (scored 0–10 with 0 representing no discomfort and 10 representing unbearable discomfort) (Appendix 8). Adherence in this study was defined as the total stimulation time recorded by the device tracker divided by the total dose prescribed (1450 minutes) and multiplied by 100. Adherence of $\geq 80\%$ (1160 minutes) was considered acceptable for inclusion within the final analysis (Baumgartner et al. 2018).

Isotonic muscular endurance of the knee extensors

In line with preliminary work described in Chapter 4, dynamic lower limb endurance was measured on a multimodal dynamometer (Primus RS, Baltimore Therapeutic Equipment, Hanover, USA) by calculating total energy expenditure (in joules) during repetitions of knee extension/flexion at a constant

cadence under a resistance of 30% of MVIC. Participants were seated on a secure chair with an 110° angle between the seat and the back of the chair and with their knee flexed at 90° (Bahadori 2020). The pivotal point of the lever was aligned with the rotation of the knee joint to maintain appropriate position during all testing. The centre of the dynamometer head was applied to the anterior tibia, 5 cm above the lateral malleolus (Bieler et al. 2014).

Participants were instructed to contract against the resistance throughout the desired arc of motion, and to complete as many repetitions as possible, at the set speed, calculated by the dynamometer as distance divided by time. Performance of each repetition was monitored through the dynamometer power output. A successful repetition consisted of completing the entire arc of motion within 2.5 seconds. When this criterion was not achieved, the dynamometer power output would drop. A drop of $\leq 75\%$ power output (as compared with the first repetition) was considered a failed repetition (Souza and Powers 2009). The test was ended after two successive failed repetitions, or the participant reported exhaustion and asked to stop. Endurance was tested on both legs, one at a time, with the left side tested first.

Maximal voluntary isometric quadriceps strength

Maximal, voluntary, isometric contraction (MVIC) of the knee extensors was measured using the dynamometer described previously. Participants were asked to perform three repetitions of three second maximal contractions of knee extension. Participants were seated on a secure chair with an 110° angle between the seat and the back of the chair and with their knee flexed at 90° (Bahadori 2020). Participants were secured with a Velcro strap positioned around their hips to limit contralateral compensation. The pivotal point of the lever was aligned with the rotation of the knee joint to maintain appropriate position during all testing. To perform knee extension, the centre of the dynamometer head was applied to the anterior tibia, 5cm above the lateral malleolus (Bieler et al. 2014). Force was automatically adjusted by the dynamometer to account for the length of the dynamometer attachment and lower limb segments distal to the joint being tested (Bahadori 2020).

Participants were given consistent verbal encouragement during each contraction for attainment of maximal performance (McNair et al. 1996) and a one-minute recovery period was observed between each maximal effort (Muff et al. 2016). If the coefficient of variation of the three tests was greater than 12.5%, the test was repeated following a period of rest to improve reliability of the study findings (Campbell M.J. 2007). A mean value from the three efforts was recorded for MVIC, and later normalised to body mass (kilograms (kg)) (N/kg), to account for the confounding influence of body weight on dynamometric measurement (Jaric 2002).

Quadriceps muscle depth

Quadriceps muscle depth was added as an outcome measure to this final study due to its reliability for measuring change in skeletal muscle mass (Pillen and van Alfen 2011). While magnetic resonance imaging (MRI) or computed tomography (CT) are the gold standard for evaluating muscle size, ultrasonography also provides a reliable and accurate measurement (Abe et al. 2015). The muscle depth of the rectus femoris and vastus intermedius were measured using a linear array ultrasound scanner (Samsung RS85). The participant was positioned supine on an examination bed with their knees in full extension (ie. anatomical zero). The transducer was placed 15 cm above the proximal border of the patella, applied with as little pressure as possible. Images of the rectus femoris and vastus intermedius were taken and subsequent depth measurements were recorded using the scanner's electronic on-screen callipers. After identifying the muscle tissue, the thickness of the quadriceps muscle was obtained by measuring the distance between the cortex of the femur, and the most superficial muscular fascia, as per the methodology of Pardo et al (Figure 17). This method has demonstrated good intra- and inter-observer reliability in 280 measurements of quadriceps thickness, providing a reliable measure of quadriceps muscle depth (Pardo et al. 2018). This study found the intra-class correlation coefficient for intra-rater reliability as 0.74 (95% CI 0.63; 0.84) at the midpoint site of the thigh, and 0.83 (95% CI 0.75; 0.9) at the two thirds site (Pardo et al. 2018). However, while every attempt was made to ensure the ultrasound measurements were conducted with the same methodology, by the same observer, intra-rater reliability was not tested for this study.

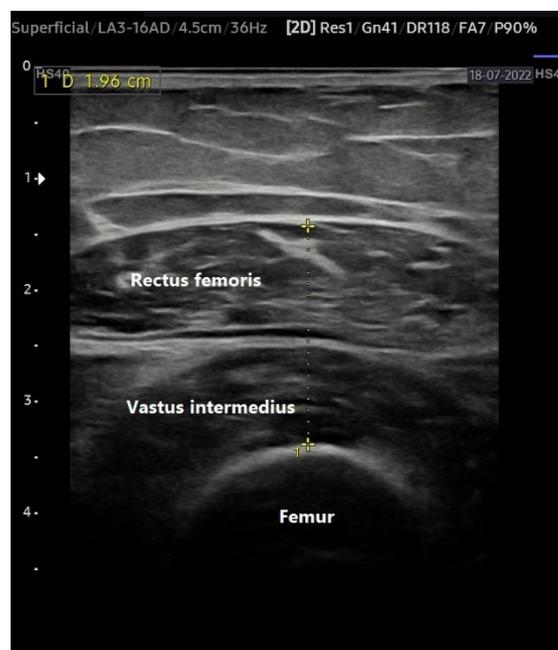


Figure 17 Example ultrasound assessment of the quadriceps femoris muscle thickness made by linear probe.

Own image

Thigh circumference

Thigh circumference was measured 15 cm above the proximal border of the patella using a tape measure, to evaluate any change in thigh size following use of the NMES device. While this method is widely used in the assessment of girth, accuracy can be affected by the tester, the tension placed on the tape measure and correct landmarking. To minimise error, the methodology used in the baseline assessment was repeated at the post-intervention assessment, whereby participants were positioned in supine, and asked to relax their legs for the measurement. The International Standards for Anthropometric Assessment, published by the International Society for the Advancement of Kinanthropometry (ISAK) were followed, whereby constant tension was achieved by ensuring that there was no indentation of the skin, yet the tape measure holds its place at the designated location (Esparza-Ros et al. 2019).

Functional performance

Consistent with preliminary work (Chapter 4), functional performance was assessed through the 40 metre (m) fast-paced walk test, the 30-second chair stand test, and a stair negotiation test (Dobson et al. 2013b). Walk speed was measured as the time taken (in seconds) to complete a 10-metre walkway four times, as quickly as possible, but at a safe pace. The 30-second chair stand test measured the number of times the participant could rise fully from chair and return to the seated position in 30 seconds. The participants' arms were crossed and held close to the chest to avoid upper body compensation. Stair negotiation was measured as the time taken in seconds to safely ascend and descend nine stairs (including turning around at the top) with a 20cm (8inch) step height, at a self-selected pace. A handrail was provided but not used unless necessary for safety. In preliminary work (Chapter 4), an 11-step stair climb test was used. However, a 9-step stair climb test has been scored as most favourable (Dobson et al. 2013a), and comparative studies in osteoarthritis often use a 9-step stair climb test, and therefore a 9 step stair climb test was used in this study to allow for comparison with the wider evidence-base.

Adverse events

Participants were asked to report any adverse events, adverse device effects or device deficiencies throughout the study and were asked about these during their telephone review, and their post-intervention testing session. These events were defined using adapted definitions from the Health Research Authority on safety reporting in medical research (The Health Research Authority 2022). An adverse event was defined as any unfavourable and unintended sign, symptom, illness, or experience that develops or worsens in severity during the study after use of the NMES device has begun. Adverse device effects were defined as any adverse event resulting from insufficient or inadequate instructions for use, deployment, implantation installation, or operation, or any malfunction of the NMES device.

This definition also includes any event resulting from user error or from intentional misuse of the NMES device. Finally, device deficiencies were defined as any malfunction of the device.

Sample Size

A power calculation was not completed as this was a feasibility study. Instead, twelve participants were chosen to take part in this feasibility study in line with recommendations that 12 participants allows a trial to provide a reliable answer to the question addressed (Julious 2005). These numbers are also sufficient to achieve an adequate estimate of the standard deviation of the proposed primary outcome measures for which to perform a power calculation to plan the next study in this research.

Data handling

Data were originally collected on paper CRFs, and later entered onto an electronic case report form (eCRF), using a secure, web-based portal (ActiPath Ltd, Dorset, UK), that is restricted to specific users and requires user authentication to access.

Analytical methods

All data were analysed using IBM SPSS Statistics version 28 (SPSS Inc., Chicago, USA), with the significance level set as $p < 0.05$. The normality of the objective data was tested using the Shapiro-Wilk test. Normally distributed data were compared from baseline to post-intervention using a two-sided paired T-Test. Data from the left knee extensor endurance test were not normally distributed and hence a Wilcoxon Signed Rank test was used to compare change from pre-intervention to post-intervention. Mean (standard deviation) and median (interquartile range (IQR)) were used to describe normally and non-normally distributed data, respectively. Effect sizes for change in means were estimated using Cohen's d (Cohen 1988), and manually calculated as Cohen's r for change in medians using the calculation $r = z/\sqrt{n}$ (Fritz et al. 2012). Interpretation of effect sizes for Cohen's d were guided by Cohen (1988) whereby 0.2 translated to a small effect, 0.5 as a medium effect and 0.8 or above equated to a large effect size. Interpretation of Cohen's r were also guided by Cohen (1988), whereby 0.1 = a small effect, 0.3 = a medium effect and 0.5 or above = a large effect. Participant feedback on the device was categorised into key themes and reported using a descriptive analysis.

8.4 Results

Twenty-eight individuals volunteered to take part in the study between 9th May 2022 and 2nd September 2022 (Figure 18). During the initial telephone consultation, 14 volunteers did not meet the inclusion criteria due to: musculoskeletal comorbidity ($n = 6$), cardiovascular comorbidity ($n = 3$), being fitted with an active medical implant ($n = 3$), neurological comorbidity ($n = 1$) and participation in voluntary strengthening exercise for the quadriceps ($n = 1$) and were excluded from the study. A total of 14 volunteers were invited to attend their initial assessment at Bournemouth University. A further two

participants were excluded due to sciatica and ongoing medial collateral ligament (MCL) pain not previously disclosed. Twelve participants completed the study and are included in this analysis. The study ended once all twelve participants had completed their post-intervention visit.

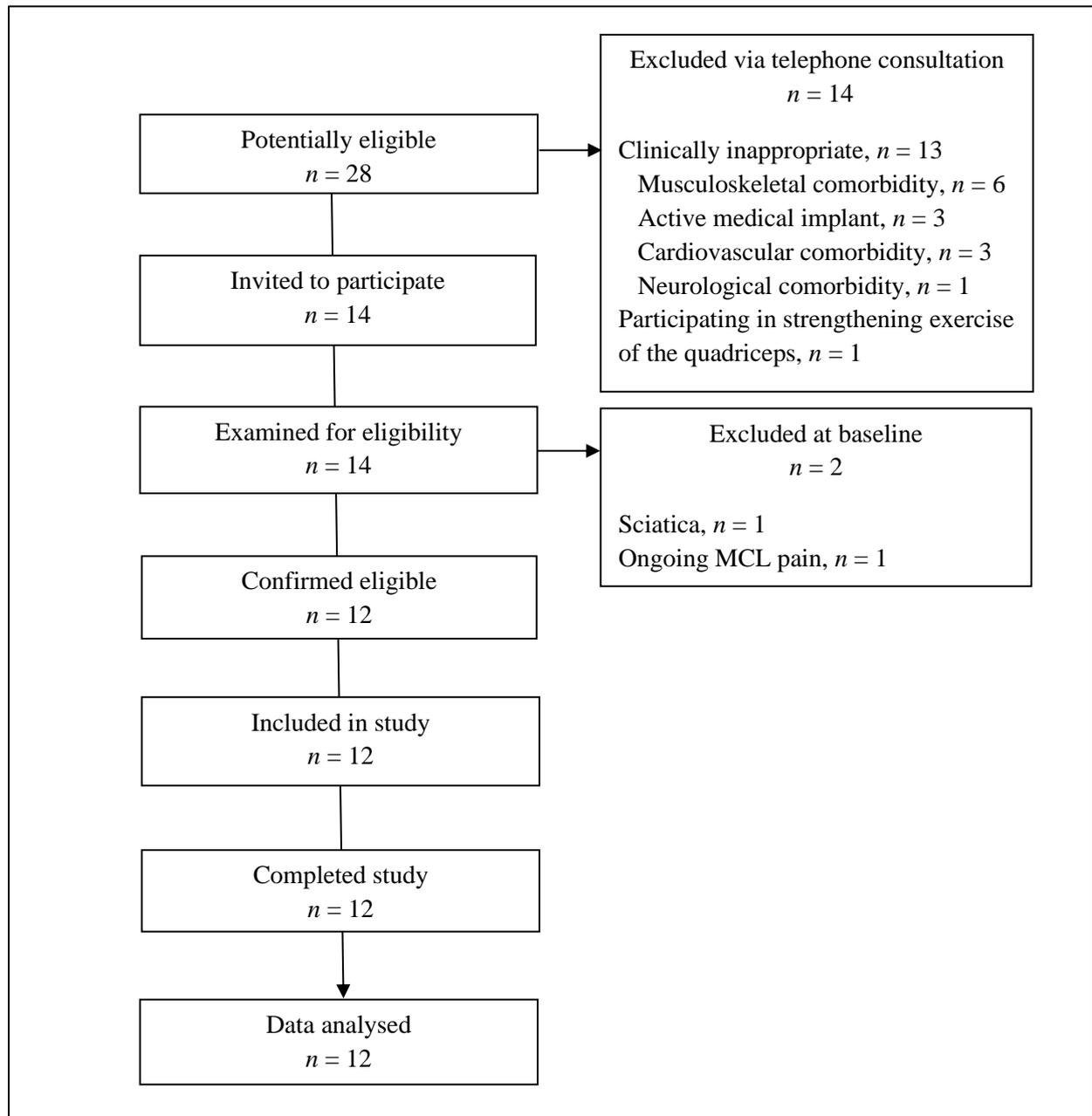


Figure 18. Flowchart of participant recruitment

Participants

Of the twelve participants, eight were female (67%) and four were male (33%). At baseline, the mean age of the participants was 72 ± 6.99 years (range 60 – 84), and their BMI was 25.40 ± 3.71 . BMI remained unchanged at the post-intervention visit, with a mean score of 25.39 ± 3.65 ($p = 0.96$). The

mean physical activity score of the participants at baseline (PASE) was 179.26 ± 61.85 , and this remained unchanged at the post-intervention visit (mean: 197.73 ± 101.23 , $p = 0.29$). No adverse events, adverse device effects or device deficiencies were reported throughout the study.

Results synthesis

Adherence

All participants completed the study and adhered to the study intervention (defined as at least 80% of the prescribed stimulation dose), with data from the device tracker suggested that the device was used for an average of 1520 ± 328 minutes (prescribed dose = 1450 minutes). Mean adherence rate was $105 \pm 23\%$, ranging from 81% - 158%, indicating that some participants were using the device for longer than prescribed. Data from the participant diaries, and the ‘turned-on’ feature of the device tracker showed that some participants chose to complete one long session of stimulation per day, rather than two shorter ones. Data from the participant diaries were consistent with the device tracker for both device usage and turned-on times. Approximate mean weekly current intensity increased linearly with the duration of the intervention (Figure 19), suggesting participant tolerance to NMES increased with time. The mean current intensity recorded over the duration of the intervention was roughly 50 ± 8 mA.

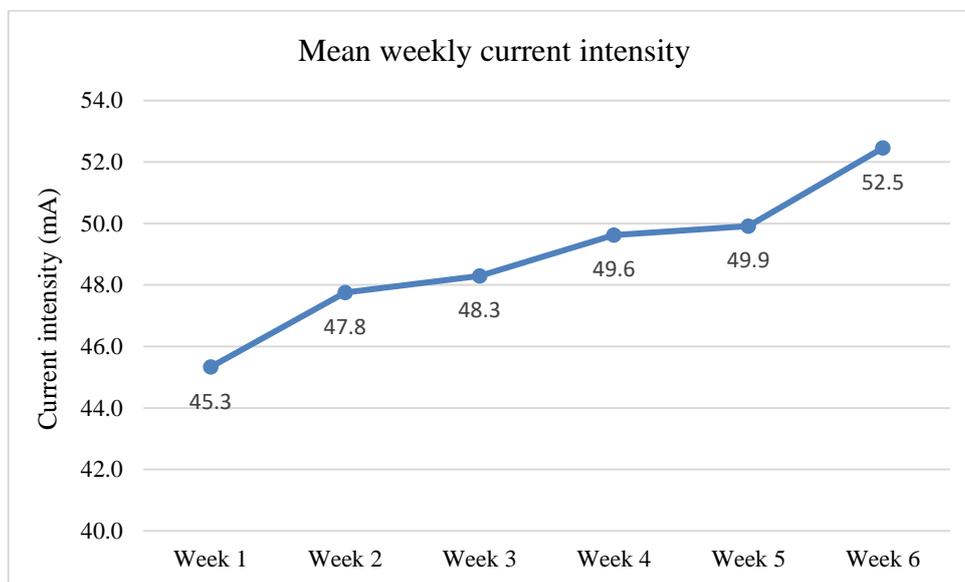


Figure 19 Mean weekly NMES current intensity (mA)

Device acceptability

The mean system usability scale score was 87.08 ± 12.96 , corresponding to grade A, which suggests that the system is excellent in terms of usability (Brooke 1986). When asked about their experience of using NMES, five participants (42%) reported that the device was really easy to use, six (50%) reported that it was easy to use, and one participant reported that it was moderately easy to use. In

terms of comfort, two participants (17%) reported that they found the device really comfortable, three (25%) comfortable, six (50%) moderately comfortable and one participant (8%) found the device uncomfortable. Regarding pain, four participants (33%) reported no pain during stimulation, five (42%) reported slight pain and three (25%) reported moderate pain. Mean self-reported discomfort extracted from the NMES diaries was 3.4 out of 10, ranging from 0 to 8.59, with 0 representing no discomfort and 10 representing unbearable discomfort. All participants reported that they would consider using NMES again, and that they would consider recommending NMES to a friend.

When participants were asked what they liked about the device, a common theme amongst responses was that the device was easy to use, and convenient to use at home or while away on holiday. Furthermore, participants reported that they enjoyed seeing the visible muscle contraction, and that this motivated them to continue with the intervention. One participant reported that they liked how easy it was to adjust the intensity of the exercise, by altering the current amplitude. Participant reported benefits of the intervention included: an improvement to their ability to walk up hills and climb stairs, reduced knee pain, increased muscle bulk, improved walking endurance and improved running ability. When asked about what they disliked, most responses were related to the use of the electrodes. For example, one participant reported that they found it difficult to apply the electrodes in the right position, and one participant said that rehydrating the electrodes was a complicated process. Two participants reported that would like to use a device without the leads so that they could walk around while stimulating their muscles although in practice this could make walking difficult. One participant reported that the 30-minute stimulation sessions felt timing consuming, however, conversely, three participants reported that they enjoyed the opportunity to exercise their muscles while sitting for 30-minutes.

Knee extensor strength

Data from the analysis of muscle function and size are presented in Table 7 ($n = 12$). Two participants lost concentration during the endurance test on their right limb, and therefore their data were excluded from this analysis, as the test end point was before the point of quadriceps fatigue. In ten participants who completed the test, mean isotonic muscular endurance of the right knee extensors was 1596 ± 989 joules at baseline, increasing by 32% to 2100 ± 1067 joules at the post-intervention assessment ($p = 0.03$), yielding a medium effect size ($d = 0.76$). On the left leg, median knee extensor endurance at baseline was 1410 joules (IQR 1012 – 2162), increasing by 62 % to 2280 joules (IQR 1285 – 3751) after the NMES intervention ($p = 0.002$), which can be interpreted as a large effect size. One outlier in this dataset likely explains the non-normal distribution of this data, whereby one participant expended 11083 joules during the endurance test. Mean MVIC of the right limb increased by 28% from 3.21 ± 1.56 N/kg at baseline to 4.12 ± 1.71 N/kg after the NMES intervention ($p = 0.02$). Similarly, mean

MVIC of the left limb increased by 32% from 3.35 ± 1.62 N/kg to 4.43 ± 1.71 N/kg ($p = 0.01$). The effect sizes of these changes were considered large using grading by Cohen (1988).

Muscle size

Quadriceps muscle depth increased in the right limb by 12% (baseline: 2.08 ± 0.67 cm, post-intervention: 2.35 ± 0.75 cm, $p = 0.005$), yielding a large effect size. Likewise, muscle depth increased by 17% in the left limb (baseline: 1.86 ± 0.52 cm, post-intervention: 2.18 ± 0.52 cm, $p = 0.01$), yielding a large effect size. Consistent with these findings, thigh circumference increased from baseline to post-intervention. The mean circumference of the right leg of participants was 49.54 ± 4.12 cm at baseline, and 50.67 ± 4.87 cm at post-intervention ($p = 0.007$), equating to a 2% increase. Likewise, at baseline the left leg of participants was 49.88 ± 4.25 cm in diameter, and 50.88 ± 4.86 cm at post-intervention ($p = 0.001$), demonstrating a 2% increase. These changes were considered large using grading by Cohen (1988).

	Baseline <i>n</i> = 12 Mean ± SD	Post-intervention <i>n</i> = 12 Mean ± SD	Difference (95% CI)	<i>p</i> value	Effect size	Percentage change from baseline to post- intervention
Right knee extensor endurance (joules)**	1596 ± 989	2100 ± 1067	505 (72 – 937)	0.03*	0.76	32%
Left knee extensor endurance (joules)***	1410 (IQR 1012 – 2162)	2280 (IQR 1285 – 3751)	870 (IQR 206 – 1743)	0.002*	0.62****	62%
Right MVIC knee extension (N/kg)	3.21 ± 1.56	4.12 ± 1.71	0.91 (0.22 – 1.60)	0.02*	0.84	28%
Left MVIC knee extension (N/kg)	3.35 ± 1.62	4.43 ± 1.71	1.08 (0.31 – 1.86)	0.01*	0.89	32%
Right quadriceps depth (cm)	2.08 ± 0.67	2.35 ± 0.75	0.27 (0.1 – 0.44)	0.005*	0.95	13%
Left quadriceps depth (cm)	1.86 ± 0.52	2.18 ± 0.57	0.32 (0.08 – 0.55)	0.01*	0.85	17%
Right thigh circumference (cm)	49.54 ± 4.12	50.67 ± 4.87	1.13 (0.38 – 1.87)	0.007*	0.96	2%
Left thigh circumference (cm)	49.88 ± 4.25	50.88 ± 4.86	1.00 (0.48 – 1.52)	0.001*	1.21	2%

Table 7 Grouped mean knee extensor endurance, MVIC, depth and circumference change from baseline to post-NMES intervention

SD = standard deviation; CI = confidence interval; MVIC = maximal voluntary isometric contraction; N/kg = Newtons/kilograms; cm = centimetres

* Indicates significant change ($p < 0.05$), ** $n = 10$, *** Median (interquartile range (IQR)), **** Cohen's r

Functional assessment

Participants demonstrated improvements in all three measures of function (30 second chair stand, 40 metre fast paced walk test, stair negotiation) from their baseline to their post-intervention assessment (Table 8). The change in the 30 s chair stand and 40 m fast paced walk scores yielded large effect sizes, and the change in stair negotiation can be graded as medium using guidance from Cohen (Cohen 1988).

	Baseline <i>n</i> = 12 Mean ± SD	Post- intervention <i>n</i> = 12 Mean ± SD	Difference in means (95% CI)	<i>p</i> value	Effect size	Percentage change from baseline to post- intervention
30 s chair stand (n)	10.83 ± 2.25	14.42 ± 4.96	3.58 (1.15 – 6.01)	0.008*	1.19	33%
40 m fast paced walk (s)	31.38 ± 4.77	28.37 ± 5.03	3.01 (1.40 – 4.62)	0.002*	0.98	10%
Stair negotiation (s)	11.01 ± 2.48	9.74 ± 1.7	1.27 (0.16 – 2.37)	0.03*	0.73	12%

Table 8 Functional assessment scores

SD = standard deviation; CI = confidence interval; (n) = number of stands; (s) = seconds

* Indicates significant change ($p < 0.05$)

8.5 Discussion

The incidence of osteoarthritis and joint replacement surgeries continues to increase locally and globally in line with the ageing population and obesity epidemic. Many patients with severe osteoarthritis demonstrate significant muscle weakness (Burgess et al. 2021c), which can limit mobility pre-surgery, and prolong recovery post-surgery. Given that current rehabilitation strategies may be ineffective at producing a level of neuromuscular activation required to induce a muscle strength adaption (Smith et al. 2009; Gavin et al. 2018), innovations are required to improve recovery. This study aimed to determine the feasibility of NMES for increasing knee extensor endurance, and subsequent functional performance, in healthy older adults, with the aim of informing future work in patients with hip osteoarthritis who may require treatment with joint replacement surgery. The objectives were to:

1. Assess recruitment, retention, and adherence rates to a six-week intervention of home-based NMES in an older adult population.
2. Determine acceptability and usability of a six-week intervention of home-based NMES to an older adult population.
3. Explore whether six weeks of home-based NMES leads to improvements in muscle endurance and maximal muscle strength.

4. Explore whether improvements in muscle endurance and maximal muscle strength translate to improvements in mobility and function.

Summary of findings

The study found that a six-week intervention of home-based NMES, applied bilaterally to the knee extensor muscle group was feasible and acceptable to a sample of healthy, older adults. In addition, the NMES intervention was successful at improving bilateral muscle endurance and maximal strength. Participants demonstrated bilateral improvements to their quadriceps muscle depth and thigh circumference. It is likely these muscular changes benefited participant mobility, given that improvements to functional ability were observed for all three tests (sit to stand, 40 m fast-paced walk and the stair negotiation test), yielding medium (stair negotiation) and large effect sizes (30 second sit-stand and 40 m fast-paced walk tests). While these results are limited by the small sample size, they provide important findings that build upon our preliminary work and can be used to inform future investigations and application of NMES.

Feasibility

The measures of feasibility included in this study answered the first and second objectives and provide promising results for future investigations and implementation of NMES into the older adult population. All participants completed the study and adhered to the NMES duration, with the mean adherence rate at $105\% \pm 23\%$, ranging from 81% - 158%, indicating that some participants were using the device for longer than prescribed. Augmentation of muscle strength through NMES can occur in a similar manner to that of resistance training, if it is prescribed with repetitions of high external load, and a high intensity of muscle contraction. In studies of older adults participating in resistance exercise, adherence rates to study interventions can be low, and decrease over time. In one study of 231 elderly women (mean age 70.5 years), adherence rate to a ten-week programme (three sessions of 50 minutes per week) was 49.7% for the aerobic exercise and 56.2% for strength training (Picorelli et al. 2014). Similarly, in a study of 56 older adults (mean age 68 years), participants were free to decide whether they continued resistance training independently after a supervised 12-week intervention (Van Roie et al. 2015). Twelve weeks after the initial intervention, less than a quarter (11-21%) of participants chose to continue with high or low resistance exercise, despite participants reporting high levels of motivation before, during and after the supervised intervention. Commonly reported barriers for continuing the exercise were: perceived lack of time (46%), being more interested in other activities (40%), seasonal reasons (40%) and financial cost (28%) (Van Roie et al. 2015).

Adherence may be even lower in older adults with osteoarthritis, due to severe pain and biomechanical changes to the joint that can alter their response to voluntary exercise (Latham and Liu

2010). In a review of eleven studies with a total of 1231 participants with chronic obstructive pulmonary disease, diabetes, cardiovascular disease, or osteoarthritis, just 33% of patients were fully adherent to an exercise programme prescribed after the completion of a supervised exercise, and 37% were partially adherent (Jansons et al. 2017). Similarly, one study found that 57.8% of participants were adherent to a three-month intervention of exercise therapy, reducing to 44.1% and 30.1% at 15 and 60 month follow up, respectively. While the data collected on adherence in the present study is only for six weeks, it provides encouraging findings for future applications of NMES. The high adherence levels may, in part, be related to the built-in adherence tracker, as participants knew their usage could be reviewed. However, participants frequently reported that the device was convenient to use while at home or while away on holiday, which may also explain the high adherence rates. When resistance training involves travelling to a gym or leisure centre, logistical, financial, and environmental barriers may impede adherence and long-term participation. With NMES the convenience of use at home, and therefore limited influence of external barriers, may encourage adherence.

Knee extensor endurance

The main and novel finding of this research is that the NMES protocol prescribed was successful in improving bilateral knee extensor endurance in older adults, answering objective 3. There is limited evidence available that advocates the use of NMES for counteracting sarcopenia in older adults and to date, most evidence has focused on maximal strength rather than muscular endurance (Langeard et al. 2017; Rahmati et al. 2021). One research group previously included a fatigue test in their evaluations of a bilateral NMES intervention compared and combined with a stair climbing intervention (Paillard et al. 2003; Paillard et al. 2004; Paillard et al. 2005a; Paillard et al. 2005b; Paillard et al. 2005c). NMES was applied to the rectus femoris and vastus medialis at a frequency of 20 Hz and a continuous pulse duration of 350 μ s four times a week for six weeks, with sessions lasting fifteen minutes. A fatigue test composing of 20 movements at 240° s⁻¹ was used to measure the effect of the NMES intervention, however, in contrast to the results of the present study, fatiguability was not improved in any of the included studies (Paillard et al. 2003; Paillard et al. 2004; Paillard et al. 2005a; Paillard et al. 2005b; Paillard et al. 2005c). While the methodology of this NMES intervention is a little unclear, it appears stimulation frequency, pulse duration and intensity, and electrode positioning, and size were like that of the present study. Therefore, it is possible that fatiguability did not improve as NMES duration was much lower (6 hours vs 25 hours) and did not progress throughout the study. To achieve fatigue resistance, long periods of stimulation are required, and the length of time the stimulator is used should be increased over time (Odstock Medical Ltd 2020), as progressive overload is required in strength training to induce muscle adaptations (Kraemer 2003). It is likely the changes observed here may translate to meaningful clinical changes, given that a true change in knee extensor work (joules)

during isokinetic knee flexion/extension performed at 60°/second in an elderly population has been reported at 24% (Parraca et al. 2022), and mean change in the right limb in the present study was 32%.

In future studies of NMES for improving knee extensor endurance in an older adult or orthopaedic population, where knee extensor endurance is the primary outcome, it is estimated that a sample size of 116 participants would be required (58 in each group) to achieve a power of 80% and a level of significance of 5%, for declaring if NMES is superior to a control group not receiving NMES. This sample size calculation is based on the mean difference between knee extensor endurance without NMES use (baseline data used as the reference group) and knee extensor endurance following six weeks of NMES use (week seven data, used as the test data), and the pooled standard deviation for both groups of data. Furthermore, this sample size is based on a superiority margin of 24%, underpinned by previous research indicating that 24% represents a true change in knee extensor work in an elderly population (Parraca et al. 2022). However, it should be noted this sample size was conducted using means, standard deviations and target differences derived from a healthy older adult population due to the absence of knee extensor endurance data in an orthopaedic population, and therefore is only approximate for future RCTs conducted in an orthopaedic population.

Maximal knee extensor strength

Maximal knee extension strength also improved by 28% in the right limb and 32% in the left. In previous evaluations of the benefits of NMES to improve maximal knee extensor strength in older adults, improvement has ranged from 18.7% (Paillard et al. 2004) to 20% (Di Filippo et al. 2017). NMES training duration ranged from 6 to 8 weeks, with an average of 3 sessions per week (Rahmati et al. 2021). Mean improvement in the present study was greater, perhaps due to the increased stimulation dose and therefore total muscle time under tension, which is the amount of time a muscle is held under tension or strain during an exercise set. Research has shown that increasing muscle time under tension can increase the acute amplitude of mitochondrial and sarcoplasmic protein synthesis, and result in robust and delayed stimulation of myofibrillar protein synthesis, creating greater hypertrophic effects (Burd et al. 2012).

Function

The findings of the functional assessment in this study suggest that improvements to knee extensor muscle endurance and maximal strength may translate into improvements to mobility and function (objective 4). If replicated in a clinical population, it is likely the change of 0.14 m/s in walking speed observed here will be meaningful, given that a change of 0.10 m/s in walking speed has been reported as a substantial change in older adults (Perera et al. 2006). While no data specific to a healthy older adult population is available, the mean improvement of 3.58 in 30s sit-to-stand score is likely to be

meaningful if replicated in a patient population. A study evaluating improvement in performance measures in people with hip osteoarthritis concluded that a change of 2-3 stands could be defined as a clinically important change (Wright et al. 2011). No comparative data were found for minimally clinical important change for the 9-step stair climb test.

The research participants in the present study were a similar age to two cohorts of older adults ($n = 53$, mean age 75.45 and 77.91 years) from a nursing home who were offered NMES of the knee extensors for a period of 6 weeks, 3 times a week, with a stimulation frequency of 100 Hz and a pulse duration of 400 μ s (Acaroz Candan et al. 2019). Current intensity was increased until a visible muscle contraction was observed and adjusted with a 5 second on/15 second off period, for a total stimulation period of 20 minutes. The participants were separated into two groups; i) short stimulation, where current was applied for 4 x 5-minute sets (SNMES), or ii) long stimulation, where current was applied for 2 x 10-minute sets (LNMES). The stimulation dose was like that of the present study in that it was applied intermittently, to replicate endurance training, but with a higher frequency (100 Hz vs 20 Hz), and with a lower total dose of stimulation. The study found that isometric quadriceps strength did not change within groups or between groups, but measures of functional ability, including 30-second chair stand scores, increased.

The authors suggest perhaps the stimulation intensity was not sufficient to reach the desired level of isometric strengthening and that the benefits to functional scores may be a result of power-producing without fatigue through selective stimulation of type II muscle fibres by intermittent NMES with 100 Hz (Acaroz Candan et al. 2019). However, evidence suggests that fibre type recruitment in nonselective in NMES (Jubeau et al. 2007), and an alternative theory has been proposed, suggesting that motor unit recruitment during NMES reflects a nonselective, spatially fixed, and temporally synchronous pattern rather than in a reversal of the physiological voluntary recruitment order (Gregory and Bickel 2005). In the present study, the mean baseline 30-s sit-to-stand score was 10.83 ± 2.25 repetitions, progressing by 33 % to 14.42 ± 4.96 repetitions, whereas improvements were smaller in the study by Acaroz Candan et al., despite both study participants having similar baseline scores. The SNMES group progressed from 10.36 ± 4.03 to 11.36 ± 3.74 repetitions (10%) ($p = 0.034$), and the LNMES increased from 10.45 ± 4.54 repetitions at baseline to 11.64 ± 4.56 ($p = 0.042$) at their post-intervention assessment (11%). These findings may, in part, be explained by differences in participant characteristics (sedentary vs independent and active). However, these findings may also be explained by the longer duration of stimulation in the present study, or a stronger current intensity used. It is possible that the higher frequency of stimulation prescribed in the study by Acaroz Candan et al. induced muscle fatigue, thereby reducing the current intensity tolerated by the participant, resulting in a lower force of muscle contraction, although current intensity is not reported. Exercise intensity is a determining factor for achieving strength gains, and much like muscle overload

intensity, the higher the NMES intensity, the greater the muscle size and strength gains (Maffiuletti 2010). Therefore, prescribing stimulation at a lower frequency may lead to greater endurance and strength gains when using NMES for a six-week period.

A systematic review published in 2017 sought to understand functional benefits of lower limb NMES for older adults and found ten studies that met the inclusion criteria (Langeard et al. 2017). Two studies with small sample sizes used NMES in isolation (Caggiano et al. 1994; Kern et al. 2014), with the remaining combining NMES with voluntary exercise. The study by Caggiano et al. included 18 participants who received four weeks of NMES applied to their right rectus femoris and vastus medialis. Participants stimulated three times a week, for an average of 18.3 minutes per session, at a frequency of between 25 and 50 Hz and pulse duration of 100 – 113 μ s, for 15 seconds on and 50 seconds off. In the study by Kern et al., participants stimulated two times a week for three weeks, then three times a week for six weeks, in sets of 3 x 10 minutes, with trains of stimulation (60 Hz) lasting 3.5 seconds, with 4.5 second off intervals. The subjects were instructed to increase the stimulation intensity until their maximum sensory tolerance level was reached. The authors report a mean stimulation intensity of 128 ± 16 mA and a voltage of 39 ± 14 V, much higher than the mean current recorded here (48.9 mA) (Kern et al. 2014). Interestingly, MVIC torque of the knee at 60° extension improved by 8.4% in the four week NMES intervention (Caggiano et al. 1994) and by 6% in the nine week intervention (Kern et al. 2014). However the participants in Kern's study were ten years older than the participants of Caggiano et al, and research has suggested that strength improvements with NMES can be greater in younger than older adults (Langeard et al. 2017). The study by Kern et al. included several outcome measures that are comparable to the present study. The five times chair rise score increased by 23.9%, around 10% less than the 33% improvement observed here. In addition, a 10 m fast-paced walk test improved by 5%, whereas participants in the present study improved their 40 m walk speed by 10%. Conversely, a 12-step stair climb test demonstrated better improvements in the study by Kern et al. (21.1%), when compared to the 12% improvement observed here using a 9-step stair climb test.

Muscle size

Differences in study populations, NMES dose and methods of evaluating muscle size make it difficult to compare changes in muscle size to the existing evidence. One RCT has previously evaluated muscle mass of the quadriceps in older adults based in a nursing home following a 16-week intervention of NMES however examined cross-sectional area (CSA), rather than muscle depth (Benavent-Caballer et al. 2014), and therefore measures of muscle size are not directly comparable. The NMES intervention involved 15 stimulation trains delivered at 50 Hz, with a training intensity reaching 40% MVC, 3 times a week (Benavent-Caballer et al. 2014). The cross-sectional area of the rectus femoris increased by 30%, as measured by ultrasonography after the NMES intervention (Benavent-Caballer et al. 2014). An observational study compared eight healthy older adults receiving

eight weeks of NMES of the quadriceps and lumbar multifidus (quadriceps: 75 Hz, 400 μ s, 40 x 6.25 s (18 minutes), three times a week) to a control group receiving no stimulation (Jandova et al. 2020). This study found CSA of the vastus lateralis to increase significantly by $11.3 \pm 15.1\%$, and muscle thickness by $6.9 \pm 6.9\%$ in the NMES group, whereas all architectural parameters significantly decreased in the control group (Jandova et al. 2020). The 13% (right leg) and 17% (left leg) increases in muscle depth observed here assimilate with existing research, and are likely a result of myofiber membrane damage and repair observed with NMES use (Moreau et al. 1995), causing muscles to increase in strength and density. The skeletal muscle size gains are similar to those achieved by resistance training in older adults, whereby a 10% increase in the cross-sectional diameter of muscle has been observed in after a training period of 6 to 9 weeks (Mayer et al. 2011).

8.6 Limitations

This study was a proof-of-concept evaluation, that aimed to assess the feasibility of NMES for improving knee extensor endurance in an older adult population. Nonetheless, the statistical power of the findings is limited due to the small sample size included. In addition, the inclusion of a control group may have strengthened the findings presented here. While it is likely the strength benefits observed in this study were a result of the NMES intervention, they may in part be related to a change in daily activities or physical activities throughout the study period. Nonetheless, data from the PASE measure suggested there was no significant change in the activity levels of participants from their baseline to post-intervention visit, and this measure includes daily activities (gardening, housework etc.), as well as exercise and sport. In addition, participants were excluded if they were participating in any form of physical activity aimed at improving knee extensor endurance, and those eligible to participate were asked not to start any new form of strength training throughout the study. Participants were encouraged to answer the usability questionnaires honestly and accurately. Nonetheless, we recognise that an element of response bias may exist, whereby participants felt they should report a favourable opinion. In addition, an element of selection bias may exist, as all participants responded to the study advert and therefore may have an interest in improving their strength. The participants included in this study are likely to be more active, and with a lower BMI, than adults with hip osteoarthritis awaiting hip replacement surgery, and therefore the results evident here may not be replicable in a clinical population. There were also limitations to the outcome measures utilised in this study. For example, an element of test-retest bias may have occurred during the post-intervention assessment, where participants were familiar with the functional assessments, or knee extensor strength tests, and therefore performed better than during their baseline assessment. In addition, while every attempt was made to ensure the ultrasound measurements were conducted with the same methodology, intra-rater reliability was not tested for this study. Finally, adherence estimates derived from research studies may differ from the actual levels of adherence in the context of clinical practice, where compliance may be much lower.

8.7 Chapter summary

This study aimed to determine the feasibility of NMES for increasing knee extensor endurance, and subsequent functional performance, in healthy older adults, with the aim of informing future work in patients with hip osteoarthritis who may require treatment with joint replacement surgery. The NMES intervention prescribed was successful in improving bilateral knee extensor endurance, MVIC, quadriceps muscle depth, and thigh circumference. It is likely these muscular changes benefited participant mobility, given the improvements observed in three functional tests (30-second sit-stand, 40 m fast-paced walk test and 9-step stair climb). Importantly, all participants adhered to the intervention, and reported favourable opinions of using the device at home. Given that current rehabilitation strategies in older adult and musculoskeletal populations may be ineffective, or unfavourable to the participant, these findings support the use of NMES in these populations and provide promising results for future research and clinical practice. Future work should involve implementing the NMES intervention described in the present study to clinical populations, before and after joint replacement surgery, to understand its effect on recovery. Furthermore, longer-term follow ups are required on adherence, to understand if compliance to NMES exceeds that of voluntary resistance exercise outside of the initial study period.