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Neuromuscular electrical stimulation as an adjunct to standard care in improving walking distances in intermittent claudication patients: the NESIC RCT

Laura Burgess, Sasha Smith, Adarsh Babber, Joseph Shalhoub, Francesca Fiorentino, Consuelo Nohpal de la Rosa, Natalia Klimowska-Nassar, David M Epstein, Daniel Pérez Troncoso, Bruce Braithwaite, Ian Chetter, James Coulston, Manjit Gohel, Robert Hinchliffe, Gerard Stansby and Alun H Davies on behalf of the NESIC trial investigators

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Neuromuscular electrical stimulation as an adjunct to standard care in improving walking distances in intermittent claudication patients: the NESIC RCT

Laura Burgess,[1] Sasha Smith,[1] Adarsh Babber,[1] Joseph Shalhoub,[1] Francesca Fiorentino,[2] Consuelo Nohpal de la Rosa,[2] Natalia Klimowska-Nassar,[1,2] David M Epstein,[3] Daniel Pérez Troncoso,[3] Bruce Braithwaite,[4] Ian Chetter,[5] James Coulston,[6] Manjit Gohel,[7] Robert Hinchliffe,[8] Gerard Stansby[9] and Alun H Davies[1*] on behalf of the NESIC trial investigators

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Abstract

Neuromuscular electrical stimulation as an adjunct to standard care in improving walking distances in intermittent claudication patients: the NESIC RCT

Laura Burgess,[1] Sasha Smith,[1] Adarsh Babber,[1] Joseph Shalhoub,[1] Francesca Fiorentino,[2] Consuelo Nohpal de la Rosa,[2] Natalia Klimowska-Nassar,[1,2] David M Epstein,[3] Daniel Pérez Troncoso,[3] Bruce Braithwaite,[4] Ian Chetter,[5] James Coulston,[6] Manjit Gohel,[7] Robert Hinchliffe,[8] Gerard Stansby[9] and Alun H Davies[1*] on behalf of the NESIC trial investigators

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Background: Peripheral arterial disease is common and associated with increased cardiovascular morbidity and mortality. While patients with peripheral arterial disease are known to benefit from supervised exercise therapy, it is not always available. Neuromuscular electrical stimulation devices may offer a similar benefit. A randomised controlled trial was required to ascertain whether such devices can benefit patients who receive supervised exercise therapy and those who do not.

Objective(s): The primary objective was to assess the mean difference in absolute walking distance at 3 months in intermittent claudication patients receiving either a neuromuscular electrical stimulation device and local standard care (intervention), or local standard care alone (control).

Design: A pragmatic, multicentre, randomised controlled trial stratified by centre.

Setting: Secondary-care National Health Service hospitals in the United Kingdom.

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Participants: Patients aged ≥18 years, with a diagnosis of intermittent claudication according to the Edinburgh Claudication Questionnaire and ankle–brachial pressure index (or stress test), without contraindications to neuromuscular electrical stimulation were deemed eligible to partake.

Interventions: Participants were randomised 1 : 1 to either local standard care or local standard care and neuromuscular electrical stimulation. Due to the nature of the intervention, it was unfeasible to blind the research nurse or participant to the study allocation.

Main outcome measures: The primary outcome measure was absolute walking distance measured by treadmill testing at 3 months. Secondary outcomes included change in initial claudication distance, quality of life, compliance with interventions and haemodynamic assessments.

Results: Two hundred patients underwent randomisation, with 160 patients having analysable primary outcome data for the intention-to-treat analysis intervention (n = 80); control (n = 80). As the data were right-censored, a Tobit regression model was used to analyse the primary outcome, utilising the square root of the absolute walking distance to accommodate the skewed data. However, as this made the data difficult to interpret, a Tobit regression model using raw absolute walking distance data was used as well. Neuromuscular electrical stimulation improved the difference in absolute walking distance at 3 months but this was not statistically significant (square root of absolute walking distance: 0.835 units, 95% confidence interval −0.67 to 2.34 units; p = 0.28/absolute walking distance raw data: 27.18 m, 95% confidence interval −26.92 to 81.28 m; p = 0.323). Supervised exercise therapy participants showed a markedly improved absolute walking distance compared with patients receiving best medical therapy only at 3 months (square root of absolute walking distance: 3.295 units 95% confidence interval 1.77 to 4.82; p < 0.001/absolute walking distance raw data: 121.71 m, 95% confidence interval 67.32 to 176.10; $p \leq 0.001$). Neuromuscular electrical stimulation significantly improved absolute walking distance at 3 months for mild claudicants (square root of absolute walking distance: 2.877 units, 95% confidence interval 0.51 to 5.25; p = 0.019/absolute walking distance raw data: 120.55 m, 95% confidence interval 16.03 to 225.06; p = 0.03) compared to the control arm. This was an unplanned (post hoc) analysis.

There were no clear differences in mechanistic measurements between the two treatment groups over the follow-up period.

Serious adverse events were evenly reported between the two groups; all being classified as either not related or unlikely to be related to the study device.

Limitations: Absolute walking distance was used as the primary outcome measure; there was a large range of baseline distances in both groups with right-skewed distribution. We did not stratify by baseline absolute walking distance for the primary outcome analysis. Additionally, only 160 patients had analysable primary outcome data due to missing treadmill data.

Conclusions: Supervised exercise therapy is an effective treatment for intermittent claudication. Neuromuscular electrical stimulation appears to be beneficial as an adjunct to supervised exercise therapy and on its own in mild claudicants.

Future work: Further studies are needed to confirm the effectiveness of neuromuscular electrical stimulation in combination with supervised exercise therapy, and in mild to moderate claudicants in a larger sample size.

Study registration: This trial is registered as ISRCTN18242823.

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List of supplementary material

Report Supplementary Material 1 Committee meeting dates

Report Supplementary Material 2 Role description for the lay patient representative

Report Supplementary Material 3 Supplementary tables and figures

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Supplementary material has been provided by the authors to support the report and any files provided at submission will have been seen by peer reviewers, but not extensively reviewed. Any supplementary material provided at a later stage in the process may not have been peer reviewed.

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List of abbreviations

AE	adverse event
ABPI	ankle–brachial pressure index
ANCOVA	analysis of covariance
AWD	absolute walking distance
BMI	body mass index
BMT	best medical therapy
CI	confidence interval
CLI	critical limb ischaemia
CONSORT	Consolidated Standards of Reporting Trials
CRN	Clinical Research Network
DU	duplex ultrasound
EA	exercise advice
ECQ	Edinburgh Claudication Questionnaire
EDC	electronic data capture
EME	Efficacy and Mechanism Evaluation
EQ-5D-5L	European Quality of Life 5-Dimension 5-Level
GP	general practitioner
IC	intermittent claudication
ICD	initial claudication distance
ICER	incremental cost-effectiveness ratio
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICQ	intermittent claudication questionnaire
IDMC	Independent Data Monitoring Committee
ITT	intention-to-treat
LDF	laser doppler flowmetry
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
MICE	multiple imputation with chained equations
MWD	maximal walking distance
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
NMES	neuromuscular electrical stimulation
PAD	peripheral arterial disease
PI	principal investigator
PIS	patient information sheet
PP	per-protocol
PPI	patient and public involvement
PT	posterior tibial
PTA	percutaneous transluminal angioplasty
QALY	quality-adjusted life-year
QoL	quality of life
R&D	research and development
RCT	randomised controlled trial
SAE	serious adverse event
SAP	Statistical Analysis Plan
SET	supervised exercise therapy

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SF-36	Short-Form Health Survey-36	TSC	Trial Steering Committee
TAMV	time average mean velocity	UK	United Kingdom
TMG	Trial Management Group	VF	volume flow

Plain language summary

Why did we conduct this research?

Patients with intermittent claudication present with pain in the lower limbs on exercising, relieved by rest. This negatively impacts on exercise tolerance and quality of life.

Initially, such patients should be offered best medical therapy, including exercise advice, and a supervised exercise therapy programme. Supervised exercise therapy involves leg and feet exercises supervised by health-care professionals and, despite evidence favouring supervised versus unsupervised exercise, are underutilised in the United Kingdom. Therefore, there remains a significant difference between recommended standard care (best medical therapy and supervised exercise therapy) and 'real-world' standard care (best medical therapy only).

Neuromuscular electrical stimulation devices have emerged as safe, portable and readily accessible, with some evidence suggesting they can improve outcomes, including pain-free walking distance and quality of life. This study investigated whether a neuromuscular electrical stimulation device improved the walking distance of patients with intermittent claudication compared to local standard care available (which may include supervised exercise therapy).

What did we do?

Two hundred patients diagnosed with intermittent claudication at 11 hospitals in England took part. A computer program randomly assigned half the patients to local standard care only, while the other half were given a neuromuscular electrical stimulation device which delivers electrical stimulation to leg and feet muscles through foot-pads, plus local standard care.

What did we find?

There was no clear difference in maximal walking distances between those who received a device and those who didn't. However, neuromuscular electrical stimulation improved walking distances in patients who attended a supervised exercise therapy programme (although not significant), and clearly improved walking distances in those patients with a good baseline upper walking limit. Supervised exercise therapy significantly improved walking distances.

What could be done next?

Future research studies should further evaluate the effectiveness of neuromuscular electrical stimulation in combination with supervised exercise therapy, and in patients who have a good baseline walking distance in a larger sample of patients with intermittent claudication.

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Scientific summary

Background

Peripheral arterial disease (PAD) is a common condition that is predominantly caused by atherosclerosis, resulting in a reduced blood flow to the affected limb. It presents a significant global health burden, affecting over 200 million people worldwide. These individuals are at higher risk of other cardiovascular events and PAD itself has its own associated sequelae – for example, ulcer development. Intermittent claudication (IC) is the commonest symptom of PAD, patients experiencing leg pain while walking which is relieved by rest. This has a significant impact on exercise tolerance and quality of life.

According to National Institute for Health and Care Excellence guidelines, all patients suffering from IC should receive both first-line treatment of best medical therapy (BMT) (including exercise advice) and supervised exercise therapy (SET). SET is known to significantly improve absolute walking distance (AWD) in IC patients but despite these guidelines, recommended care for the first-line management of claudication is significantly below standard, largely due to lack of National Health Service capability. Without a demonstrable benefit of non-invasive strategies for the management of IC, there is an increased likelihood of invasive treatment options.

Neuromuscular electrical stimulation (NMES) is an emerging technology and such devices are readily accessible and can be used in the patient's own home. Although some evidence of the efficacy of NMES in the management of patients with IC exists, in improving both functional and quality-of-life measures, further high-quality research is required. The NESIC (A Multicenter Randomised Controlled Study: Does **N**euromuscular **E**lectrical **S**timulation Improve the Absolute Walking Distance in Patients with **I**ntermittent **C**laudication (NESIC) compared to best available treatment?) study provides an evidence base for the efficacy of the REVITIVE IX™ (Actegy Health Ltd, Bracknell, UK) device in the non-invasive management of claudicants and assesses the cost-effectiveness of the device compared to SET.

Objectives (list of research questions)

1. Primary objective: To assess the clinical efficacy of a NMES device as an adjunct to the local standard care available at the study randomisation sites to improve AWD in patients with IC.
2. Secondary objectives:
    a. To understand the underlying mechanisms for change in clinical and subjective outcomes in the form of lower-limb gross (duplex ultrasound) and superficial haemodynamic assessment (laser doppler flowmetry)
    b. To determine compliance with NMES device and SET programme
    c. To compare quality of life between those receiving local standard care alone and those receiving both local standard care and NMES
    d. To assess the actual cost-effectiveness of the NMES device compared to SET.

Methods

Design

A multicentre, pragmatic, randomised clinical trial to compare the mean difference in AWD in patients with IC who are given NMES in addition to local standard care and those receiving local standard care only.

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Setting

Eleven secondary-care NHS hospitals across England; a combination of centres with and without established provision of SET.

Participants

Between March 2018 and 17 March 2020, 200 participants were randomised into the NESIC trial. Follow-up was completed on 31 March 2021. Written informed consent was obtained from all participants, who then underwent eligibility assessments. Participants, as defined by the inclusion and exclusion criteria, were randomised 1 : 1 to either local standard care alone (standard care), or NMES and local standard care (intervention).

Inclusion criteria

- positive Edinburgh Claudication Questionnaire
- ankle–brachial pressure index <0.9 OR positive stress test (fall in ankle pressure >30 mmHg, 40 seconds post 1 minute treadmill at 10% gradient, 4 km/hour)
- able to give informed consent to participate in the trial after reading the patient information documentation
- age ≥18 years.

Exclusion criteria

- severe IC requiring invasive intervention as determined by the treating clinician
- critical limb ischaemia as defined by the European Consensus Document
- comorbid disease prohibiting walking on a treadmill or taking part in SET
- able to walk for longer than 15 minutes on the study treadmill assessment
- have attended SET classes in the previous 6 months
- popliteal entrapment syndrome
- commenced vascular-symptom-specific medication in previous 6 months – for example, naftidrofuryl oxalate, cilostazol
- pregnancy
- any implanted electronic, cardiac or defibrillator device
- acute deep vein thrombosis
- broken or bleeding skin, including leg ulceration
- peripheral neuropathy
- recent lower-limb injury or lower back pain
- already using a NMES device.

Randomisation

Randomisation (1 : 1) was web-based and hosted by Oracle Health Sciences InForm™ (Oracle®; Health Sciences, Austin, TX, USA) electronic data capture on an Oracle platform. Randomisation used random block size and was stratified by centres.

Interventions

The NMES device (REVITIVE IX) can be used in the patient's own home. It delivers a 30-minute pre-programmed session of electrical stimulation to the lower-limb muscles through foot pads while the patient is in a seated position. The user controls the intensity of the impulses, and therapeutic benefit is deemed to occur when impulses are sufficient to cause contraction of the calf muscles, increasing venous return to the heart. The IsoRocker feature allows the device to tilt back and forth as the muscles

contract and relax. The device is to be used for at least one 30-minute session daily (up to a maximum of six sessions) for 3 months (treatment period). Diabetic patients are to use the device for a minimum of two 30-minute sessions daily for the duration of the treatment period to better reflect the evidence supporting the diabetic patient group and improvement of their symptoms.

A SET programme is usually led by a physiotherapist or allied health-care provider supervising exercise, usually within the physiotherapy gymnasium with equipment including a treadmill, steps and walking cones. SET classes usually involve a circuit of lower-limb exercises, for a minimum of 30 minutes per week, and usually over a 3-month duration.

Outcomes and follow-up

The primary outcome was AWD at 3 months, measured by treadmill testing. Secondary outcomes included quality of life over 12 months as measured by generic health-related quality of life tools, European Quality of Life 5-Dimensions 5-Level (EQ-5D-5L®) (EuroQol Group, Rotterdam, The Netherlands), Short-Form Health Survey-36 (SF-36®) (RAND Health Care, Santa Monica, CA, USA) and the intermittent claudication questionnaire; compliance with NMES and SET as measured against self-report participant diaries and device data loggers; change in initial claudication distance measured by treadmill testing; and haemodynamic assessments measured by duplex ultrasound and laser doppler flowmetry.

Participants in both groups were followed up for 12 months post randomisation. In-person visits were performed at screening/baseline (randomisation), 3 months, 6 months and 12 months. The treadmill assessment (Gardner-Skinner protocol) and laser doppler flowmetry of the foot were completed at each visit and the duplex ultrasound was performed by a vascular scientist at baseline and 3 months only. Self-report health resource-use participant diaries were completed throughout the 12-month duration of the study. Additionally, the self-report exercise diaries were completed by all participants for 3 months or for the duration of the SET programme, and the device compliance diaries were completed by participants randomised to NMES for the duration of the treatment period. A device experience questionnaire was completed at 3 months for participants in the NMES arm of the trial.

The quality-of-life questionnaires were administered at baseline and each follow-up either in person, via the telephone or via post. Participant follow-up is summarised in *Appendix 1*.

Due to the COVID-19 crisis, a substantial amendment was submitted to Ethics in April 2020 to allow all follow-up visits to take place remotely (i.e. over the telephone completely or in combination with postal questionnaires) in the event that the participant was unable to attend in clinic or the site was unable to accommodate the on-site visit. Missed (physical) assessments as a result of a remote visit were rescheduled at a later date as a separate on-site visit, where possible. If an on-site visit was rescheduled at a later date, all quality-of-life questionnaires that were completed remotely were repeated at the on-site visit.

Results (research findings)

Two hundred participants underwent randomisation and 160 were included in the intention-to-treat primary analysis [intervention (n = 80); control (n = 80)]. NMES improved AWD in patients with IC following the 3-month treatment period but this was not statistically significant [square root of AWD: 0.835 units, 95% confidence interval (CI) −0.67 to 2.34; p = 0.276/AWD raw data: 27.18 m, 95% CI −26.92 to 81.28; p = 0.323]. Participants who had access to a SET programme showed a clear improvement in AWD compared with patients who received BMT only at 3 months (square root of AWD: 3.295 units, 95% CI 1.77 to 4.82; p < 0.001/AWD raw data: 121.1 m, 95% CI 67.32 to 176.10; p < 0.001). Improvements in the AWD at 3 months were seen when NMES was used in combination with SET, but this was not significant (square root of AWD: 1.724 units, 95% CI −0.56 to 4.01; p = 0.137/AWD raw data: 64.26 units, 95% CI −20.03 to 148.54; p = 0.13). NMES significantly improved AWD at 3 months for patients who could walk for more than

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340 m at baseline (square root of AWD: 2.877 units, 95% CI 0.51 to 5.25; $p = 0.019$/AWD raw data: 120.55 m, 95% CI 16.03 to 225.06; $p = 0.03$) compared to the control arm.

Mechanistic findings of the laser doppler flowmetry found no clear differences in blood flux between the two treatment groups over the 12-month follow-up period, nor any significant differences in volume flow or time average mean velocity (duplex ultrasound) groups at 3 months.

Serious adverse events ($n = 29$) were reported in 24 participants, with all events being classified as either not related or unlikely to be related to the study device. The number of SAEs in the treatment arm was 13 and 16 in the control arm. Most of the events required hospitalisation; there were four deaths.

Conclusions

The results of the NESIC trial indicate that SET is the most effective treatment option for patients with IC. Although not significant, NMES improves walking distances when used in combination with a SET programme, and significantly improves AWD in mild claudicants.

Implications for health care

Findings from this trial suggest that all IC patients should have access to a SET programme and changes to such programmes may need to be made to encourage and/or retain participants. NMES may be an effective adjunct to SET and in patients with a good baseline walking distance.

Recommendations for research (numbered in priority order)

1. Randomised controlled trial of NMES as an adjunct to SET in IC patients stratified by baseline AWD, as the NESIC study showed promise of non-invasive effectiveness in mild and/or moderate claudicants at improving walking distances, but larger numbers are required to validate this finding.
2. Research to examine the poor patient motivation and adherence to SET, as SET is clearly an effective treatment option for claudicants as seen in this study and many other studies but uptake/compliance remains an issue.
3. Research to evaluate the long-term effectiveness of SET programmes on maximal walking distance (MWD) and secondary outcomes such as quality of life and long-term engagement in physical activity. The NESIC study showed the effectiveness of SET at 12 months at improving AWD but longer-term follow-up is required to evaluate whether this is sustained years later. Previous studies have shown mixed results on the impact of SET on other outcomes, such as quality of life, and therefore further research is required.

Study registration

This trial is registered as ISRCTN18242823.

Funding

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Chapter 1 Introduction

Background: intermittent claudication

Peripheral arterial disease (PAD) is the chronic obstruction of the arteries supplying the lower limbs caused by atherosclerosis. The incidence of PAD increases with age, and in the United Kingdom (UK) around one in five people over the age of 60 have some form of PAD.[1] Risk factors include smoking, hypercholesterolaemia, hypertension and diabetes. These individuals are more likely to suffer comorbid conditions such as heart attacks and stroke.[2]

Intermittent claudication (IC) is the most common manifestation of symptomatic PAD, presenting as pain or weakness with walking that is relieved with rest. This is functionally debilitating and results in a poor quality of life (QoL).[3] IC symptoms remain stable for the majority of patients but around 5–10% may develop critical limb ischaemia (CLI). CLI is characterised by a severe obstruction in the circulation of the lower extremities, ischaemic pain and tissue loss (gangrene/ulceration). In some cases, this may eventually lead to limb amputation, with associated changes to QoL. Those patients with diabetes are at a higher risk. In the UK, PAD is the single largest cause of limb amputation.[1]

Treatment options for intermittent claudication

The National Institute for Health and Care Excellence (NICE) guidelines recommend that patients with IC should be offered support and treatment regarding the secondary prevention of cardiovascular disease. This includes exercise advice (EA), lipid modification and statin treatment, antiplatelet therapy as well as the prevention, diagnosis and management of high blood pressure and diabetes, known as best medical therapy (BMT). They should also be offered a supervised exercise therapy (SET) programme as a first-line treatment option.[4] SET classes usually involve a circuit of lower-limb exercises under the supervision of a health-care professional, for a minimum of 30 minutes per week usually over 3 months duration. Only if BMT and SET have not led to a satisfactory improvement in IC symptoms is surgical intervention offered for suitable patients (angioplasty, primary stent placement or bypass).[4]

There are a number of vasoactive drugs licensed to treat the symptoms of IC specifically when conservative treatment has been ineffective, with NICE recommending naftidrofuryl oxalate as the preferred treatment[4] as it is the most cost-effective and efficacious (up to 60% improvement).[5]

Summary of current research

There is a strong evidence base supporting the initial management of IC as per NICE guidance,[4] including BMT and SET to increase the pain-free walking distance.[6]

A Cochrane systematic review of the impact of SET on walking time or distance was carried out by Bendermacher *et al*. in 2006,[7] repeated in 2013 by Fokkenrood *et al*.,[6] and updated again in 2018 by Hageman *et al*.[8] The latter review included parallel-group randomised controlled trial (RCT) data comparing SET to home-based exercise therapy and walking advice in patients with IC. Twenty-one studies with a total of 1400 participants were randomised and followed up between 6 weeks and 2 years, with the primary outcome measure being maximal walking distance or time (MWD/T). There was a significant improvement in MWD/T compared with home-based exercise therapy and walking advice, with overall standardised mean differences at 3 months of 0.80 [95% confidence interval (CI)

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0.53 to 1.07; $p < 0.00001$; high-quality evidence]. This translates to an improvement in MWD of 210 m in the SET group.[8]

Despite its beneficial effects, SET is underutilised in the UK. Recommended care for the first-line management of claudication is significantly below standard largely due to lack of National Health Service (NHS) funding. In 2017, 89 Vascular Society of Great Britain and Ireland members completed a survey, representing 59 (57%) of the 97 vascular units registering data on the National Vascular Register. Of the respondents, 37 (41.6%) members reported that they had access to SET, which equates to only 22 (38.5%) of the vascular units having access to a supervised exercise programme for IC patients.[9] A 2021 audit[10] showed that only 36% of UK vascular units have access to SET for PAD patients, and only four are fully compliant with current NICE guidelines. With increasing constraints on NHS budgets, poor access to SET is unlikely to improve. Where available, the authors noted poor uptake and adherence, with reasons including lack of transportation to SET centres, personal travel expenditure, inflexibility of classes and absence from work being cited.

To attend SET for 2 hours per week for 3 months duration costs approximately £288 per patient, equating to approximately £1608 per quality-adjusted life-year (QALY) gained.[3] This includes the time of a physiotherapist or allied health-care provider supervising within the physiotherapy gymnasium with equipment including a treadmill, steps and walking cones. This is for a finite treatment period as dictated by the SET and does not include the patient's own costs.[3]

Clinical practice is variable between clinicians for prescribing vasoactive medications.[11] Additionally, their efficacy in clinical trials has been variable,[12,13] there are associated side effects such as diarrhoea and vomiting[14] and they are contraindicated in certain conditions such as hyperoxaluria or recurrent calcium-containing stones.[15] A systematic review by Momsen *et al.*[13] concluded that there are a number of drugs that improve MWD but with limited benefits.

Without a demonstrable benefit of non-invasive strategies for the management of IC, there is an increased likelihood of invasive treatment options. These procedures are expensive, for example bypass surgery costs approximately £8857.00, procedure cost.[16] Additionally, patients undergoing surgery have more complications and so may be more of a clinical and economic burden on the NHS.[17] A cost-effectiveness study conducted by Djerf *et al.*[18] concluded that the costs of revascularisation in conjunction with BMT in IC patients were approximately four times higher than for those receiving BMT alone. The incremental cost-effectiveness ratio (ICER) of revascularisation exceeded that of the NICE guidelines.[18]

The true standard of care, therefore, for the majority of patients with IC in the UK and Ireland is BMT only. Therefore, adjuncts to these therapies must be explored.

Neuromuscular electrical stimulation

Emerging technologies include neuromuscular electrical stimulation (NMES) devices, which may be beneficial in some people suffering with IC by improving the distance walked before symptomatic limitation and improve QoL.[19] While evidence is limited, a systematic review of five trials conducted by Williams *et al.*[20] investigating different NMES devices used as a treatment option for IC patients demonstrated an improvement in MWD by up to 150% at 4 weeks of intervention.

Moreover, a proof-of-concept pilot study of 20 participants with IC showed a significant improvement in absolute walking distance (AWD) of 85 m (102.3 m vs. 187.2 m, $p < 0.01$) and initial claudication distance (ICD) of 38 m (50.5 m vs. 88.2 m, $p < 0.01$) in a 6-week period. Using a REVITIVE IX (Actegy Health Ltd, Bracknell, UK) device, all patients underwent 30 minutes of NMES daily at their own convenience, in the comfort of their homes. Repeated measures were then taken at the 6-week

follow-up appointment. In addition to this functional improvement, there were significant improvements in both validated generic EQ-5D-5L scores (0.5427 vs. 0.6443, $p < 0.005$) and disease-specific intermittent claudication questionnaire (ICQ) (44.3 vs. 35.21, $p < 0.002$) QoL questionnaire scores at 6 weeks.[19] Compliance to the device during the 6-week intervention period was 98.5% as assessed by patient-recorded diaries. A subsequent RCT compared SET (group A) versus SET plus NMES (group B). The AWD and ICD both significantly increased over the 6-week treatment period in both groups, with the change in ICD in group B being significantly greater than that in group A (40.4 vs. 7.5 m, respectively; $p = 0.012$).[21]

Technological advances have allowed portable, inexpensive and safe electrical-stimulation units to be developed which can be used in the patient's own home.[22] These devices deliver therapeutic levels of intensity to cause contraction of the calf muscles in similar ways to intermittent limb compression and may have similar beneficial effects.[20]

Mechanistic evaluation of the device

This study also aimed to evaluate the potential underlying mechanism by which NMES may improve walking distances in patients with IC. A number of devices that perform compression have been developed, the most common of these being intermittent pneumatic compression devices. Studies evaluating such devices have shown functional and symptomatic benefits in patients with IC.[20] These work by applying high-level pneumatic compression to the foot and/or calf, reducing the venous leg pressure and consequently increasing flow rate in the popliteal artery and stimulating the release of vasodilators.[23,24] It is hypothesised that these physiological responses are responsible for improving claudication symptoms. This mechanism of action may be similar for NMES devices. The RCT by Babber *et al.*[21] found significant increases in volume flow (VF) and time average mean velocity (TAMV) when the device was switched on at baseline and at week 6, although this was not maintained after device cessation.

Further haemodynamic assessment is therefore required in this study to help better understand and assist in developing future technology to optimise the use of this mechanism for patient benefit.

Rationale for the NESIC study

Supervised exercise, BMT, medications and radiological and surgical intervention are all effective therapies[20] for treating IC. However, mortality rates related to PAD are rising,[20] with a death rate of 20% within 5 years following diagnosis,[25] and there are limitations to their use.

Current NICE guidelines[4] for the initial management of IC are impractical. Although evidence-based, there is a significant underutilisation of SET, an evidence-based treatment modality that can significantly improve functional ability.[6] The underutilisation is driven by a chronic lack of NHS funding to support staff and set up resources for an exercise programme as well as due to compliance, as patients often need to travel long distances at their own expense on a regular basis in order to benefit from attending an exercise class. Patients who are in employment often decline an invitation for SET, do not attend or require significant time off work to attend. The more realistic picture of current initial management of IC is BMT only.

Invasive procedures such as bypass or angioplasty (using a balloon to widen a narrowed artery) to restore blood flow carry risks of operative complications and often patients are unsuitable for such interventions.[20] These procedures are also expensive and if these measures fail, a major amputation is the usual fate, with associated changes to QoL.[26]

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An effective, non-invasive modality that will promote compliance with treatment or act as a valid alternative for the majority unable to access SET is therefore required. The per-unit price of a commercially available NMES device is approximately £250 and therefore cheaper than the per-person cost of attending SET, which is also limited to a treatment duration of 3–6 months.[6] The NESIC trial aimed to determine:

Is there an adjuvant benefit of NMES to locally available therapy, including SET or BMT only? Is NMES cost-effective in this role compared to SET? Is there potential for NMES use as first-line management of patients with IC?

Chapter 2 Methods

Primary objectives

The primary objective was to compare the mean difference in AWD at 3 months in patients with IC receiving a NMES device and local standard care (intervention), compared with local standard care alone (control).

Secondary objectives

Other objectives included:

- change in ICD
- compliance with NMES during the 3-month treatment period
- compliance with the localised SET programme at SET centres
- to understand the underlying mechanisms for change in clinical and subjective outcomes in the form of lower-limb gross and superficial haemodynamic assessment
- QoL – change in European Quality of Life 5-Dimension 5-Level (EQ-5D-5L®) (EuroQol Group, Rotterdam, The Netherlands) and Short-Form Health Survey-36 (SF-36®) (RAND Health Care, Santa Monica, CA, USA) (validated generic QoL tools) and the ICQ over 12 months from baseline
- to assess the cost-effectiveness of the NMES device compared to SET.

Trial design

A multicentre, pragmatic, randomised clinical trial to compare the mean difference in AWD at 3 months from baseline in patients with IC. Participants were randomised 1 : 1 to either:

1. local standard care (control)
2. NMES device and local standard care (intervention).

Changes to the trial design

The NESIC trial aimed to recruit 96 patients in each arm (192 in total): SET arm (96 patients) and non-SET arm (96 patients). The SET recruitment target (96) was met in June 2019 but continued in order to replace participants who had been excluded post randomisation (108 SET patients were successfully randomised in total).

Recruitment into the non-SET arm continued and was extended until 31 March 2020. This extension of recruitment was approved by the National Institute for Health and Care Research (NIHR) Efficacy and Mechanism Evaluation (EME), and they advised to wait to submit the contractual agreement until after recruitment had completed so actual amounts requested could be confirmed However, due to the COVID-19 crisis, recruitment was formally paused early on 20 March 2020. At this point 92 non-SET patients had been randomised and only four more patients were required to meet the recruitment target. Following advice from the Independent Data Monitoring Committee (IDMC) and the Trial Steering Committee (TSC), recruitment did not restart and was formally closed as it was not deemed worthwhile to keep recruitment open in the existing COVID-19 climate for four more participants

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and it was likely that sufficient power had already been achieved. This was discussed with the EME Programme Director, who supported the decision to not reopen recruitment. A total of 200 patients were successfully randomised into the study.

In November 2020 the EME programme team approved a contract variation, awarding an 8-month extension to enable sites to continue to exclusively recruit non-SET participants and to ensure all recruited participants are followed up 12 months post randomisation. This was a small costed extension to cover salaries and estates/infrastructure costs; as there was an underspend on the study (largely on patient and Trial Manager travel), these funds were vired to cover most of the costs.

Amendments to the protocol

Substantial amendments to the trial protocol were submitted after the initial approval, to clarify statistical changes, dosage clarification for diabetic patients, addition of extra participating centres and in light of the COVID-19 crisis, to permit remote visits.

Version 2.0, dated 5 December 2017: an amendment was made to change the organisation name of the Bristol site that was mistakenly incorrect in version 1.0; and the statistical analysis section was revised as per Medicines and Healthcare Products Regulatory Agency (MHRA) request to detail how subjects who drop out of the study will be analysed and the approach to the analysis of the primary outcome was amended (randomisation stratification variable 'centre').

Version 3.0, dated 22 March 2018: typographical errors corrected; and dosage clarification for diabetic patients [recommended a minimum dosage of two (2) × 30 minute sessions per day to better reflect the evidence supporting the diabetic patient group and improvement of their symptoms, rather than a minimum of one (1) × 30 minute daily session].

Version 4.0, dated 7 September 2018: addition of three new participating NHS organisations.

Version 5.0, dated 9 September 2019: addition of additional exclusion criterions to document the criteria that have been followed throughout the duration of the trial; and to permit authorised SET centres to recruit non-SET patients to help aid recruitment into this arm of the trial (patients at SET centres will first be offered the opportunity to attend the SET classes, and only if they do not wish to attend these classes will they be offered the opportunity to participate in the trial as a non-SET patient).

Version 6.0, dated 24 March 2020: an amendment to allow 3-month, 6-month and 12-month visits to take place remotely (i.e. over the telephone completely or in combination with postal questionnaires) in the event that the participant is unable to attend in clinic or the site is unable to accommodate the on-site visit. This was particularly important in light of the COVID-19 pandemic where on-site visits may not be possible.

Sponsorship

The trial was sponsored by Imperial College London.

Study management

Trial Management Group

The Trial Management Group (TMG) comprised Professor Alun H Davies (as Chief Investigator), Ms Laura Burgess (as Trial Manager), Ms Sasha Smith [as Trial Manager (maternity cover)], Ms Consuelo

Nohpal de la Rosa (as Statistician), Dr Francesca Fiorentino (as Senior Statistician) and Ms Natalia Klimowska-Nassar (as Operations Manager).

Trial Steering Committee

In line with NIHR research governance guidelines, an independent TSC was established to oversee the conduct of the trial. The membership consisted of three independent members (see *Acknowledgements*), as well as the Chief Investigator, Trial Manager, study statisticians and lay patient co-applicant. The committee met, on average, every 6 months or more regularly if required, as decided by the committee. For the meeting dates see *Report Supplementary Material 1*.

Independent Data Monitoring Committee

The IDMC was established as per the EME IDMC terms of reference, to monitor study data and safety. The membership comprised three independent members (see *Acknowledgements*). The members met once prior to the start of the trial to agree the IDMC Charter and then, on average, every 6 months to review recruitment, retention and unblinded comparative data.

Participants

All patients aged ≥18 years, with a diagnosis of IC according to the Edinburgh Claudication Questionnaire (ECQ) and ankle–brachial pressure index (ABPI) (or stress test), were eligible to be included in the trial.

Intervention

Participants in both arms were given local standard care, which includes BMT (such as EA, smoking cessation, etc.) and may include a SET programme, dependent on the Trust, in line with NICE guideline CG147.[4] The SET programme is localised to the Trust (and was not standardised in the study protocol). *Table 1* includes the full list of SET sites and their specific SET programme. The SET classes usually involve a circuit of specific lower-limb exercises, supervised by a health-care professional.

Patients in the NMES (intervention) arm also received a REVITIVE IX device (Model: RIX Ref: 1379, Software Version: 2.0). The device is a Class IIa active medical device intended for electrical stimulation of the lower leg in healthy individuals. The indications for use are certified under the Medical Devices Directive 93/42/EEC. The components of the REVITIVE IX device can be found in *Figure 1*.

TABLE 1 Supervised exercise therapy localised programmes

	Sessions per week	Number of months	Total number of sessions
Imperial College Healthcare NHS Trust	1	6	24
North Bristol NHS Trust	2	3	24
Hull and East Yorkshire Hospitals NHS Foundation Trust	3	3	36
University Hospital Southampton NHS Foundation Trust	1	2	8
Dorset County Hospital NHS Foundation Trust	1	2	8
The Royal Bournemouth & Christchurch Hospitals NHS Foundation Trust	1	3	12

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FIGURE 1 Parts and controls of REVITIVE IX. C, foot pads; D, light-emitting diode display panel; E, time-setting controls; F, foot pad intensity controls; G, electrode pad intensity controls; H, power button; I, location of accessory and power sockets; J, IsoRocker. Source: reproduced with permission from *REVITIVE IX Circulation Booster: User's Manual*. Bracknell, United Kingdom: Actegy Health Ltd; 2016.

The REVITIVE IX device comes with an alternating current / direct current power adaptor and remote control.

The NMES device delivers electrical stimulation to the participant's feet via a pair of cushioned foot pads, while they are seated. The IsoRocker feature allows the device to rock back and forth, ensuring adequate stimulation of the calf and foot muscles.

The device is intended for home use for one pre-programmed 30-minute session per day, up to no more than six sessions per day. All devices used in the trial were labelled with the wording 'exclusively for clinical investigation' as per MHRA request.

Participants in the standard-of-care (control) arm of the trial received a device at their 12-month study visit.

Inclusion criteria

- positive ECQ
- ABPI <0.9 OR positive stress test (fall in ankle pressure >30 mmHg, 40 seconds post 1 minute treadmill at 10% gradient, 4 km/hour)
- able to give informed consent to participate in the trial after reading the patient information documentation
- age ≥18 years.

Exclusion criteria

- severe IC requiring invasive intervention as determined by the treating clinician
- CLI as defined by the European Consensus Document
- comorbid disease prohibiting walking on a treadmill or taking part in SET
- able to walk for longer than 15 minutes on the study treadmill assessment
- have attended SET classes in the previous 6 months
- popliteal entrapment syndrome
- commenced vascular-symptom-specific medication in previous 6 months, for example, naftidrofuryl oxalate, cilostazol
- pregnancy

- any implanted electronic, cardiac or defibrillator device
- acute deep-vein thrombosis
- broken or bleeding skin, including leg ulceration
- peripheral neuropathy
- recent lower-limb injury or lower back pain
- already using a NMES device.

Sample size

Assuming that the mean AWD in the control group is 200 m following the 3-month treatment period[27] with a common equal standard deviation of 120 m,[28] and anticipating a 10% rate of loss to follow-up, we estimated that 192 participants would be required to have 90% power with a two-sided alpha level of 5% to detect a difference of 60 m in the mean AWD at 3 months between the intervention and the control group.

Randomisation and treatment allocation

Consenting participants were registered on the web-based data-entry system maintained by Oracle Health Sciences InForm™ electronic data capture (EDC) on an Oracle platform. The randomisation was web-based and blocked with random block size 2, 4 and 6 and stratified by centres. Once eligibility was confirmed, randomisation was performed at the local hospital site by the research nurse prior to any study-related assessments being performed. Participants were randomised to one of the two arms of the trial and assigned a pseudo-anonymised study number unique to each subject enrolled on the study.

Blinding

Due to the nature of the intervention, it was unfeasible to blind the research nurse or participant to the study allocation and a sham device was deemed both impractical and difficult to administer, especially with the REVITIVE IX device causing visual ankle movement. Where possible, a blinded assessor carried out the treadmill test independently and the patient was not given a final score to prevent bias. The senior statistician remained blinded throughout the study.

Settings and location

All participants were recruited from the vascular clinics of 11 secondary-care NHS Trusts throughout England: Imperial College Healthcare NHS Trust; Cambridge University Hospitals NHS Foundation Trust; North Bristol NHS Trust; The Newcastle Upon Tyne Hospitals NHS Foundation Trust; Hull and East Yorkshire Hospitals NHS Foundation Trust; Somerset NHS Foundation Trust (formerly Taunton and Somerset NHS Foundation Trust); University Hospital Southampton NHS Foundation Trust; Nottingham University Hospitals NHS Trust; Dorset County Hospital NHS Foundation Trust; St George's University Hospitals NHS Foundation Trust; The Royal Bournemouth & Christchurch Hospitals NHS Foundation Trust. For a list of participating hospitals see *Acknowledgements*, *Local research teams*.

Sites were selected based on their ability to recruit to the trial, the willingness of the principal investigator (PI) to randomise into the trial and their proven track record in research.

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Screening and participant identification

Adult patients presenting to vascular outpatient clinics with a diagnosis of IC were screened by the direct health-care team for eligibility at recruiting centres. The study Research Nurse/Coordinator was notified, who then approached the patient with an information leaflet either in person, via the telephone or by post. Patients were given appropriate time to consider enrolment before consenting assessments were performed.

Recruiting sites also displayed posters describing the study at vascular clinics and the study was presented at many multidisciplinary team meetings to promote awareness among staff.

Anonymous screening logs were completed for all participating sites to log the reasons for non-inclusion along with a minimum data set of age, sex and ABPI (with the permission of the patient). These were frequently sent to the Trial Coordinating Centre to continually monitor recruitment.

Informed consent

Patients who expressed interest in the trial after reading the information leaflet were provided with a patient information sheet (PIS) by the study Research Nurse to consider the trial participation. Consent to enter the study was sought from each subject after a full verbal explanation was given. Potential participants were given ample time to consider study enrolment and ask any questions they may have had.

Written informed consent was obtained from each participant at the screening/baseline visit. The PIS and the consent form both refer to the possibility of linking their data with appropriate databases, including Hospital Episode Statistics and the National Vascular Database, as well as long-term follow-up and access to their NHS records for these purposes. With consent, a letter was also sent to the participant's general practitioner (GP). A copy of the letter was filed in the Investigator Site File (ISF). The original copy of the signed consent form and PIS were filed in the participant's local research file (source documents) and a copy was given to the participant.

Written informed consent was obtained before the subject was enrolled in the study.

Baseline assessments

Following written informed consent from the participant, baseline data were collected by the Research Nurse/Coordinator using the case report form. Assessments included the following.

Patient demographic details

Demographic details were obtained including date of birth, gender, ethnicity and working status. Women of childbearing potential were required to take a urine pregnancy test to ensure they did not breach the exclusion criteria.

Ankle–brachial pressure index/stress test

The brachial blood pressure of both arms was taken using a manual blood pressure monitor cuff and Doppler, using the highest reading to calculate the ABPI. The pressures were recorded after 5 minutes of rest in a supine position on a couch. The systolic blood pressures of the dorsalis pedalis (DP) and posterior tibial (PT) of both ankles using the cuff and doppler method were also obtained, using the highest reading to calculate the ABPI. The ratio of the systolic brachial and ankle pressures formed the total ABPI measurement. Participants needed an ABPI <0.9 to be eligible for the study or to have a positive stress test. The stress test was performed by measuring the fall in ankle pressure 40 seconds post a 1-minute treadmill at 10% gradient, 4 km/hour. If the fall in pressure was >30 mmHg, this was deemed a positive stress test.

Edinburgh Claudication Questionnaire

The Edinburgh Claudication Questionnaire (ECQ) is a validated questionnaire for diagnosing IC. Claudicants were deemed as being typical (indicates pain in the calf, regardless of whether pain is also indicated in other sites) or atypical (pain is indicated in the thigh or buttock, in the absence of any calf pain). Participants were not considered to have claudication if pain was indicated in the hamstrings, feet, shins or joints or appeared to radiate, in the absence of any calf pain.

Peripheral pulses

Peripheral pulses of the common femoral, popliteal, dorsal pedalis and posterior tibial were taken for both legs. It was noted whether they were aneurysmal, normal, reduced or absent.

Treadmill assessment

The Gardner-Skinner protocol was used. The treadmill started at 3.2 km/hour at 0% gradient; every 2 minutes, the incline increased by 2%. Participants indicated when they first felt claudication pain (ICD) and the assessment was stopped when the participant could no longer continue due to lower-limb pain (AWD). The results of the test were not disclosed to the participant to prevent bias. Patients able to walk for further than 15 minutes on the treadmill at baseline were excluded from the study.

Vital signs and lifestyle

Weight and height were recorded; the database auto-calculated body mass index (BMI), as well as a pulse and blood pressure measurement. Lifestyle details were collected, including smoking status and alcohol consumption.

Medications and medical history

Significant medical history and current medications were recorded.

Haemodynamic assessments

The laser doppler flowmetry (LDF) and duplex ultrasound (DU) assessments were performed simultaneously. Participants had a minimum 10-minute resting period, in a seated position, before recordings began. They sat in an armed chair with their back at a slight angle for the duration of the LDF/DU measurements. Patient's knees were at a 90° angle so that participants in the intervention group could effectively use the REVITIVE IX device during the assessments.

Laser doppler flowmetry

Laser doppler flowmetry was used to assess skin surface temperature and flux (superficial skin perfusion; measured in arbitrary units). A single-channel moorVMS-LDF device (Moor Instruments, Axminster, UK) was used, with one probe placed on the dorsal aspect of the most affected foot using a single-use sticky adhesive disc. Once the probe was placed, measurements were continuously recorded via the LDF software. For control participants, this was at rest for a duration of 3 minutes. For device participants, this was at rest, for 30 minutes during device use, and for 5 minutes following device cessation.

Duplex ultrasound

An arterial ultrasound probe on a DU machine (linear array L12-3 MHz) was used to assess the common femoral artery diameter (cm), time-adjusted mean velocity (TAMV, cm/s) and blood VF (cc/minute) of the most affected limb. The probe was placed approximately 3 cm from the origin of the profunda and measurements were obtained at a 60° insonation angle. For control participants, this was at rest for a duration of 3 minutes. For device participants, these parameters were measured at rest, at 15 and 30 minutes into device use and at 1 and 5 minutes after device cessation. At each time-point, the average of three measurements per time-point was taken for accuracy.

Quality-of-life questionnaires

Patient-reported QoL questionnaires were completed at baseline, prior to informing the participant of the treatment allocation to prevent bias.

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European Quality of Life 5-Dimension 5-Level questionnaire

EQ-5D-5L is an instrument to measure generic health-related QoL. The descriptive element consists of five domains: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Participants were asked to select the most appropriate statement from the following five options: no problems, slight problems, moderate problems, severe problems or extreme problems. The visual analogue scale recorded the participant's self-rated health on a vertical visual analogue scale labelled 'the best health you can imagine' at the top to 'the worst health you can imagine' at the bottom of the scale. Respondents were asked to 'mark an X on the scale to indicate how your health is TODAY'. This was used as a quantitative measure of health outcome.

Short-Form Health Survey-36

Short-Form Health Survey-36 is a widely accepted generic tool to measure health-related QoL. It consists of 36 questions which cover eight domains of health: physical functioning, physical role, bodily pain, general health, vitality, social functioning, emotional role and mental health.

Intermittent claudication questionnaire

The ICQ is a disease-specific tool for assessing health-related QoL in patients with IC. It is a self-administered questionnaire that consists of a 5-point adjectival scale with 16 items scoring between 0 and 100 (higher scores indicating better health).

Once eligibility was confirmed, participants were randomised on a 1 : 1 ratio to either the intervention or control arm of the study, via the EDC (InForm). Following randomisation, participants were given the following materials:

- A resource-use diary to complete health-care resource use during the duration of the study. A new copy of the diary was given to participants at their scheduled baseline, month 3 and month 6 visits and collected by the research team at their subsequent visit.
- An exercise diary to complete number of minutes of exercise completed in the participant's own time (completed for the 3-month treatment period). At SET centres, participants also recorded the number of SET sessions attended (completed for the duration of the SET programme).
- A device compliance diary (intervention arm only) to record device use details for the treatment period.
- A wallet card reminder indicating the contact details of the local research nurse.

Compliance

Compliance to each of the interventions [EA (part of BMT), SET and NMES] was measured separately to determine the complier/non-complier classification. For each of the treatment groups compliance was defined as follows:

- EA: compliant if completed 75% or more of recommended level of EA (75% of minutes performing exercises recommended by centre).
- SET: compliant if attended 50% or more SET sessions held by centre.
- NMES: compliant if completed 75% or more of recommended level of NMES usage.

Adverse events

The Research Nurse/Coordinator collected all adverse events (AEs) during the duration of the study. AEs were followed up according to local practice until the event had stabilised or resolved. All AEs were assessed for causality and expectedness in relation to the device. The site staff collected occurrences of AEs during follow-up visits, either in person or via telephone or hospital notes.

Serious adverse events

As per the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice guidelines, serious adverse events (SAEs) were defined as those adverse events that led to a death; led to a serious deterioration in health that either resulted in a life-threatening illness or injury, or resulted in a permanent impairment of a body structure or a body function, or required inpatient hospitalisation or prolongation of existing hospitalisation, or resulted in medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function; led to fetal distress, fetal death or a congenital abnormality or birth defect; or led to other important medical events in the opinion of the responsible investigator. This included device deficiencies that might have led to a SAE if (1) suitable action had not been taken or (2) intervention had not been made or (3) circumstances had been less fortunate.

The site staff collected all occurrences of SAEs during follow-up visits, either in person or via telephone or hospital notes. Such events were collected on the EDC system within 24 hours of the study staff becoming aware of the event and reviewed by the local PI and Chief Investigator.

All SAEs were also reported by the Trial Manager to the Sponsor and reviewed by the DMC. SAEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, Geneva, Switzerland) Version 24.0 [URL: www.meddra.org (accessed 7 June 2021)]. MedDRA® is a standardised medical terminology developed by ICH that is used to code medical events in humans.

Follow-up

All randomised participants were followed up until completion of the trial, defined as:

- 12 months post randomisation
- withdrawal from the trial
- death.

Participants in both groups were followed up at 3 months (end of treatment phase), 6 months and 12 months post randomisation. Assessments at this time point included:

- treadmill test
- ABPI/peripheral pulse examination
- QoL questionnaires as per baseline (EQ-5D-5L, SF-36 and ICQ)
- duplex ultrasonography (the DU performed at baseline and 3-month follow-up visit only)
- LDF [the LDF assessment was only performed for 3 minutes at rest at the 6- and 12-month follow-up visit (in both groups)]
- review of participant resource-use diary
- collection of device compliance diary (performed at the 3-month follow-up visit only)
- collection of exercise diary (collected at the 3-month follow-up visit and 6-month visit if the patient continued to attend SET classes following the 3-month visit)
- collection of AEs or SAEs
- drug history review.

The 12-month follow-up appointment marked the end of the study participation. Device participants were able to keep the REVITIVE IX device and control participants were given a device to keep at their 12-month visit.

If consented, patients received weekly text message reminders during the treatment phase to remind them to complete their diaries and attend SET or follow EA.

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If the participant was unable to attend the follow-up visit in person or the site was unable to accommodate an on-site visit, the visit could take place remotely (i.e. over the telephone completely or in combination with postal questionnaires). Every effort was made to invite participants back for an on-site visit following a remote visit to complete missed physical assessments, where possible. Sites clearly documented the mode of follow-up that took place.

Participant communications

Participants were kept up-to-date on study progress via Facebook (Meta Platforms, Inc., Menlo Park, CA, USA) and Twitter (Twitter, Inc., San Francisco, CA, USA) accounts. A newsletter summarising the main results from the NESIC trial was also sent to non-withdrawn participants.

Statistical methods

A detailed plan for the analysis of the study outcome data is included in the Statistical Analysis Plan (SAP), which was written and signed off before any final data analysis was commenced. The statistical package STATA version 17 was used to conduct all the analyses undertaken.

All the statistical methods used in the analysis were tested to check if the model's assumptions were met. Normal distribution of variables was checked by visual inspection using Q–Q plots as well as by using the Shapiro–Wilk test, while homoscedasticity was only visually assessed.

All statistical tests were two-tailed with a 5% significance level.

Additional analyses were undertaken for the raw data (of the variables that were transformed to meet normality assumptions, particularly AWD and ICD) to help with the interpretation. However, these results should be interpreted with caution as the assumption of normality is violated.

Analysis population

All analyses for the primary and secondary outcomes were conducted using complete-cases analysis for the intention-to-treat (ITT) population and per-protocol (PP) population. The ITT population includes all randomised patients after eligibility was confirmed, while the PP population excludes patients who did not attend any centre-specific SET classes. Analyses for the PP population are found in *Report Supplementary Material 3*.

Primary outcome

The primary outcome of AWD at 3 months was analysed using a Tobit regression model to incorporate the right-censored data and estimate the difference in the absolute distance walked between treatment (NMES + BMT and NMES + BMT + SET) and control (BMT and BMT + SET) at 3 months.

Participants who walked more than 15 minutes on the treadmill during any follow-up had their AWD censored to 790 m.

The Tobit regression for the AWD at 3 months included AWD at baseline, a treatment indicator (treatment = 1 vs. control = 0) and type of centre (SET = 1 vs. non-SET = 0) as covariates. As the data collected for AWD showed a right-skewed distribution, several transformation options were explored. A square-root transformation of the data was found to present a normal distribution. To help with the interpretation, two Tobit regression models were used; Model 1 used the raw data of AWD. For Model 2, the square roots of the AWD both at baseline and at 3 months were used for the Tobit regression. As a secondary analysis of the primary end point, we estimated the difference between the groups in the proportion of patients that increased the AWD at 3 months by 60 m (or more) and 100 m (or more) from baseline using a chi-squared test.

A multilevel Tobit model for right-censored data was used to investigate the difference in AWD between the two treatment groups at 3, 6 and 12 months where AWD at baseline measurement, treatment (treatment = 1 vs. control = 0), time, time × treatment interaction, type of centre (SET vs. non-SET), age, gender (male = 1 vs. female = 0), BMI and smoking status (current smoker, former smoker, never smoked) were included as fixed effects and patient as a random effect. Two multilevel Tobit models were used; Model 1 used the raw data of AWD to help with interpretation while Model 2 used the square-root transformation to normalise the data.

Additionally, models for the Tobit regression and the multilevel Tobit models were performed to explore the effect of covariate centre indicator (1 to 12) and were added to the analysis.

Right-censoring was set up at 28.106939 for the square root of AWD and at 790 m for the raw data.

Secondary outcomes

Initial claudication distance

The secondary outcome (ICD), measured at baseline, 3, 6 and 12 months, was analysed using a multilevel Tobit model to incorporate the right-censored data. The square root of ICD was used as the raw data showed a right-skewed distribution.

The multilevel Tobit model included ICD at baseline measurement, treatment (treatment = 1 vs. control = 0), time, time × treatment interaction, type of centre (SET vs. non-SET), age, gender (male = 1 vs. female = 0), BMI and smoking status (current smoker, former smoker, never smoked) as fixed effects and patient as random effect. Two multilevel Tobit models were used; Model 1 used the raw data of ICD to help with interpretation while Model 2 used the square-root transformation of ICD to normalise the data.

A secondary analysis for ICD was done to estimate the difference between groups in the proportion of patients who increased ICD at 3 months by 60 m (or more) and 100 m (or more) from baseline using a chi-squared test.

Additionally, two more models were created to explore the effect when the centre indicator (1 to 12) was included in the multilevel Tobit models.

Haemodynamic assessments

Duplex ultrasonography

Analysis for duplex ultrasonography (DU) is composed of two measurements: VF and TAMV. The DU measurements of VF and TAMV from the haemodynamic assessment, for one leg (either the left or right) at 3 months, were analysed using separate linear regression models. These linear regression models were used to compare the mean VF and mean TAMV, between the intervention group and the control group, using the baseline value of the specific measurement, treatment, type of centre, age, gender and BMI as covariates.

As the data collected showed a right-skewed distribution, the square root of VF and TAMV was used for the analysis. In addition, 10 cases were excluded from the analysis as they were identified as outliers.

Two models for each duplex ultrasonography measurement (VF and TAMV) were created; Model 1 used the raw data to help with interpretation while Model 2 used square-root transformations.

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Laser doppler flowmetry

Laser doppler flowmetry, a measurement of blood flux, was analysed using an analysis of covariance (ANCOVA) for repeated measurement at 3, 6 and 12 months. A log transformation was used for the blood flux analysis.

The ANCOVA was used to assess the difference between the treatment and control, using the log transformation of LDF at baseline, treatment, time, treatment × time (interaction) as covariates.

The full measurements collected from two patients and specific measurements for five others were identified as outliers, so these measurements were removed from the LDF analysis.

Ankle–brachial pressure index

Mixed models were used for right and left ABPI. As the data collected showed a skewed distribution, a log transformation for the right and left (ABPI) was used for the analyses. Two outliers were identified and removed from the analysis.

The mixed models were performed to investigate the effect of the treatment indicator on the changes over time (3, 6 and 12 months), treating patient as a random effect, while the baseline measurement of log right and log left ABPI, treatment, time and interaction of time × treatment were treated as fixed effects.

Quality of life

Multilevel models for each of the QoL scores (ICQ), EQ-5D-5L (health scale and health index) and SF-36, were performed to investigate changes in QoL over time. The mixed-effect models assessed the difference between treatment and control, using centre and patients as a random effect and the baseline measurement of each overall scores' dimension, treatment, time and treatment × time interaction as fixed effects.

Compliance

Compliance to each of the interventions [EA (part of BMT), SET and NMES] were measured separately to determine the complier/non-complier classification. We investigated whether there were differences in the proportions of patients complying by setting a threshold for compliance a priori, during the SAP writing stage, and then comparing the proportions. For each of the treatment groups compliance was defined as follows:

- EA: compliant if completed 75% or more of recommended level of EA (75% of minutes performing exercises recommended by centre).
- SET: compliant if attended 50% or more SET sessions held by centre.
- NMES: compliant if completed 75% or more of recommended level of NMES usage.

Then compliance was dichotomised, coding 'Yes, complied' if the patient complied with the recommended threshold treatment and 'No' if the patient did not comply. The overall classification of compliance was obtained by combining the compliance classifications for the three instruments (device, SET and EA), with compliance being necessary for all treatments a patient was assigned in order for that patient's overall compliance to be recorded as 'Yes'.

The SAP stated that compliance would be analysed using causal methods, but this was not done as the TSC independent statistician advised that CACE analysis should only be performed if there was a difference in SET uptake between the groups. The trial did not have a difference in SET, adverse event (AE) or NMES uptake, so we did not perform CACE analysis for compliance.

Instead, a chi-squared test was performed to examine if there was a difference between treatment and control when comparing compliers and non-compliers.

Subgroup analysis

Subgroup analysis to investigate the effect of the intervention among NMES + SET + BMT, NMES + BMT, SET + BMT, BMT was performed. Seven subgroup analyses were performed in the ITT population for the primary outcome of AWD, measured at 3 months using Tobit regression models with AWD at baseline, treatment, subgroup and treatment × subgroup as covariates.

Five of these subgroup analyses were originally described in the SAP and two were added later as post hoc analyses.

The subgroup effect was based on the interaction term between treatment and subgroup, but it was not included in the Tobit models for Subgroup 2 through Subgroup 7 due to problems of collinearity.

Post hoc analyses

New classification of compliance

A post hoc analysis was performed using only the compliance rules for SET and NMES, ignoring the AE compliance classification as all participants received EA. The analysis consisted of selecting only the patients who complied within the new classification and using two Tobit regression models to estimate the difference in AWD between treatments. One model used raw AWD data at 3 months and the other used the transformed square root of AWD at 3 months.

Absolute walking distance stratification

A second post hoc analysis was performed looking at the stratification of the baseline AWD measurement. The AWD at baseline was divided into three strati: short, medium and long distances (set at <25%, 25–75% and >75%, respectively) using the descriptive statistics. For each stratum a Tobit regression for the transformed right-censored AWD at 3 months was performed. A Wilcoxon rank-sum test for comparison between the treatment and control for AWD at baseline was also performed using the median, as the data showed a right-skewed distribution. For the transformed square-root AWD, a *t*-test was performed.

Missing data

Missing data for the primary end-point AWD and the secondary end points (ICD and QoL) were imputed.

The pattern of missing data was examined. The mechanism of missingness was verified, and the assumption was made that the data were missing at random (MAR). The missing values were imputed using Multiple Imputation (MI) STATA syntax with chained equations (10 imputations) and predictive mean matching (knn = 5). All the transformed variables and covariates used in the specified model for each outcome were included in the imputation model. Models for imputed data are included in the *Report Supplementary Material 3*.

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Chapter 3 Results

Study recruitment

Recruitment commenced in March 2018 and ceased at the end of March 2020. In total 200 participants were recruited from 11 study centres. *Table 2* shows the total number of participants recruited per centre. *Figure 2* shows the trajectory of recruitment over the study period. At trial commencement, the monthly target recruitment was 1–2 participants/months across the eight study centres (24 in total from each site). To help aid recruitment, a further three study centres were activated in November 2018–January 2019, each with a target of 10 participants each.

Participant flow

The Consolidated Standards of Reporting Trials (CONSORT) diagram is shown in *Figure 3*. There were 1410 patients assessed for eligibility. Of these 1210 participants were excluded; 326 had an ABPI ≥ 0.9, 166 had a comorbid disease prohibiting treadmill assessment and/or attending the SET programme, 163 declined to participate and 159 had severe IC requiring invasive intervention. See *Table 3* for further details. In total, 200 participants were randomised (with 10 included with a positive stress test) and 10 were classified as post-randomisation exclusions. The reasons were that the participant completed the baseline treadmill assessment (walked for longer than the permitted 15 minutes) (n = 5); participant did not complete baseline treadmill test (n = 2); participant could not walk at the required speed in the baseline treadmill test (n = 1); participant randomised but withdrew before completing the baseline visit (n = 1) and participant violated exclusion criteria (ECQ) (n = 1). In the treatment (device) group, 98 participants were randomised and included in the study and in the control group, 102 participants were randomised and included in the study.

Baseline characteristics for the overall population are shown in *Table 4*. The mean age in the treatment group (NMES + BMT and NMES + BMT + SET) was 68 years and 67 years in the control group (BMT and BMT + SET). In the treatment group, 76% of participants were male and 71% were male in the control group. The mean BMI in the treatment group was 28 kg/m^2 and 29 kg/m^2 (both overweight) in the control group; the majority were former smokers (70% in the treatment group and 59% in the control group) and had a medical history of hypertension and hypercholesterolaemia.

Treatment received

Overall, there were 11 patients (5 in the device group and 6 in the control group) who did not receive the allocated treatment. In the intervention group, five participants were randomised using the incorrect list (incorrect allocation from BMT + SET + NMES to BMT + SET), and in the control group five participants were randomised using the incorrect list (incorrect allocation from BMT + SET to BMT), with a further participant having purchased and used a device following randomisation.

Compliance

Compliance to each of the interventions [EA (part of BMT), SET and NMES] was measured separately. Details of compliance can be found in *Table 5*. Compliance to EA was the lowest (52.1%) but had the highest percentage of missing data (20.5%). Compliance to SET and the device were similar (69.7% and 73.9%, respectively).

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TABLE 2 Recruitment by centre for overall cohort

	Treatment[a] *n* = 98	Control[b] *n* = 102	Total *N* = 200
Imperial College Healthcare NHS Trust	14	16	30
Cambridge University Hospitals NHS Foundation Trust	7	8	15
North Bristol NHS Trust	6	7	13
The Newcastle Upon Tyne Hospitals NHS Foundation Trust	15	14	29
Hull and East Yorkshire Hospitals NHS Foundation Trust	21	21	42
Somerset NHS Foundation Trust	12	12	24
University Hospital Southampton NHS Foundation Trust	2	2	4
Nottingham University Hospitals NHS Trust	5	5	10
Dorset County Hospital NHS Foundation Trust	8	8	16
St George's University Hospitals NHS Foundation Trust	5	5	10
The Royal Bournemouth & Christchurch Hospitals NHS Foundation Trust	3	4	7

a Treatment group includes BMT + NMES and BMT + SET + NMES.
b Control group includes BMT and BMT + SET.

Note
Values are numbers.

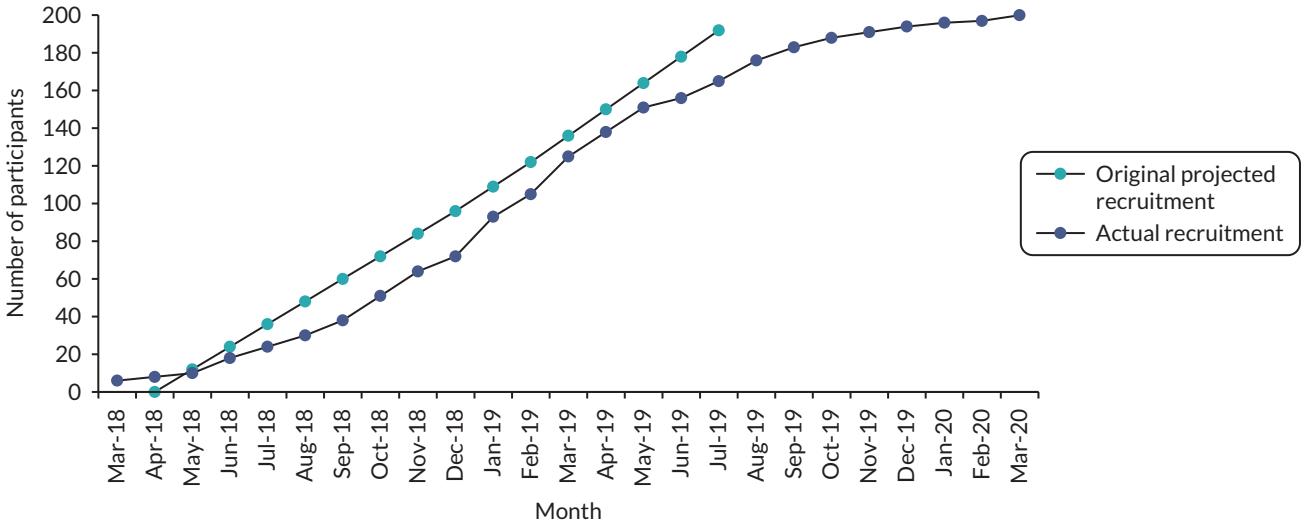


FIGURE 2 Recruitment graph.

Table 5 was used to classify each patient as either complier or not complier by combining the classifications depending on the treatment assigned (BMT + SET, BMT + SET + NMES, BMT and BMT + NMES). There were 42 out of 190 (22.1%) patients with missing information in the general compliance classification.

Table 6 shows that 40 patients (54.1%) complied with the treatment assigned in the treatment arm, while 46 patients (62.2%) complied in the control arm. There was no statistically significant difference in the proportions of compliers between treatment and control as the difference was −8.1 with a 95% CI of −23.9 to 7.7%; $p = 0.32$.

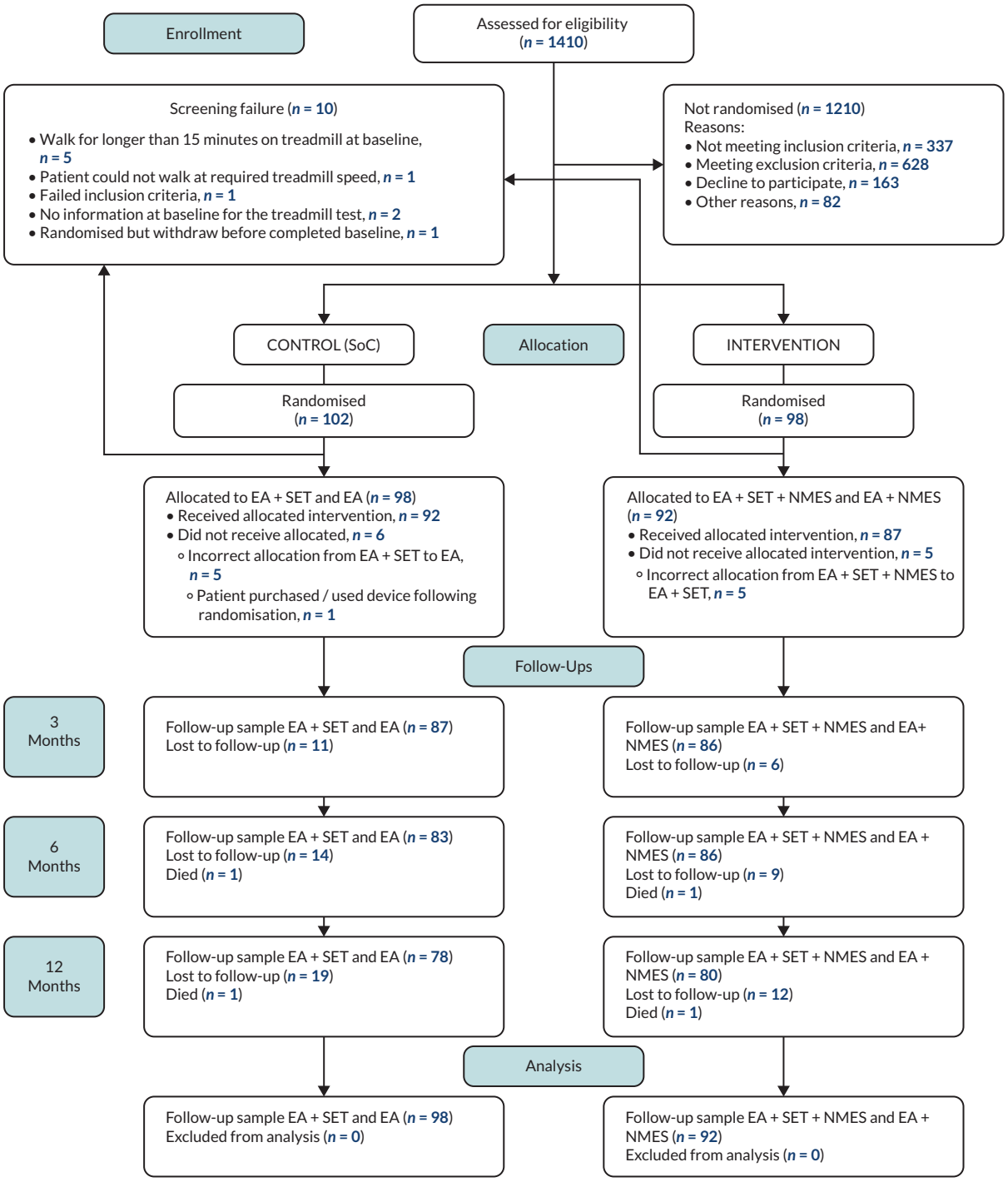


FIGURE 3 Consolidated Standards of Reporting Trials diagram of the trial population. The number of participants who had been lost to follow-up and had died by each time point are presented.

Follow-up

Primary outcome

Two hundred patients were randomised, with 160 patients having analysable primary outcome data (both at baseline and 3 months). The ITT analysis was carried out using the data of those 160 (complete cases), with the AWD at 3 months right-censored for 12 participants.

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TABLE 3 Reasons for non-inclusion

	N
ABPI ≥ 0.9	326
Comorbid disease prohibiting treadmill assessment/SET	166
Declined to participate	163
Severe IC requiring invasive intervention	159
Commenced vascular-symptom-specific medication in previous 6 months	91
Other reason	82
Walked for longer than 15 minutes on baseline treadmill test	52
Implanted electronic, cardiac or defibrillator device	37
Peripheral neuropathy	31
Already using a NMES device	24
Broken or bleeding skin/ulcer	23
Completed SET classes in previous 6 months	19
Recent lower-limb injury/lower back pain	18
Negative ECQ	11
CLI	6
Popliteal entrapment syndrome	2

Note
Values are numbers.

TABLE 4 Baseline characteristics of the trial participants[a]

Characteristic	Treatment[b] *N* = 92	Control[c] *N* = 98
Age (years)	68.17 ± 8.84	67.44 ± 9.44
BMI[d]	28.10 ± 5.12	28.63 ± 6.66
Sex, *n* (%)		
Female	22 (24)	28 (29)
Male	70 (76)	70 (71)
Smoking status, *n* (%)		
Current	22 (24)	34 (35)
Former	64 (70)	58 (59)
Never	6 (7)	6 (6)
Race, *n* (%)		
White	87 (95)	90 (92)
Asian	3 (3)	3 (3)
Black	1 (1)	3 (3)
Other	1 (1)	2 (2)
Medical history, *n* (%)		
Hypertension	65 (71)	63 (64)

continued

TABLE 4 Baseline characteristics of the trial participants[a] (*continued*)

Characteristic	Treatment[b] *N* = 92	Control[c] *N* = 98
Stroke	9 (10)	9 (9)
Myocardial infarction	15 (16)	17 (17)
Hypercholesterolaemia	68 (74)	64 (65)
Angina	10 (11)	13 (13)
Diabetes	21 (23)	26 (27)
Bypass revascularisation	5 (5)	12 (12)
Angio revascularisation	14 (15)	25 (26)
Medication, *n* (%)		
Antiplatelets	75 (82)	79 (81)
Glycoprotein IIB IIIA antagonists	92 (100)	98 (100)
Statin	80 (87)	81 (83)
Anticoagulant	10 (11)	15 (15)
Antihypertensives	66 (72)	65 (66)
ABPI[e]		
Right	0.72 ± 0.18	0.76 ± 0.21
Left	0.76 ± 0.21	0.77 ± 0.22
Retired		
No	24 (26)	29 (30)
Yes	68 (74)	69 (70)
Work status[f]		
Higher managerial and professional occupations	3 (13)	5 (17)
Intermediate occupations (e.g. clerical, sales, service)	5 (21)	4 (14)
Lower managerial and professional occupations	8 (33)	1 (3)
Lower supervisory and technical occupations	1 (4)	1 (3)
Never worked or long-term unemployed	2 (8)	7 (24)
Routine occupations	4 (17)	6 (21)
Other occupations	1 (4)	5 (17)
Performance limited due to IC		
A little	7 (29)	9 (31)
A lot	3 (13)	4 (14)
Not at all	12 (50)	9 (31)
Missing (number of patients)	2 (8)	7 (24)

a Plus–minus values are means ± SD. No significant differences were identified between the treatment groups in any baseline variable. Percentages may not total 100 because of rounding.
b Treatment group includes BMT + NMES and BMT + SET + NMES.
c Control group includes BMT and BMT + SET.
d The BMI is the weight in kilograms divided by the square of the height in metres.
e Information on ABPI was missing for two patients in the treatment group (left and right ABPI) and two and one patient(s) in the control arm (right and left ABPI), respectively.
f Only people who are not retired are reported.

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TABLE 5 Summary of patients who complied with SET, NMES and EA for the ITT population

Compliance	Total (*N*)
EA	***N* = 190**
Yes	99 (52)
No	52 (27)
Missing	39 (21)
SET	***N* = 99**
Yes	69 (70)
No	19 (19)
Missing	11 (11)
NMES	***N* = 92**
Yes	68 (74)
No	12 (13)
Missing	12 (13)

Note
Values are *n* (%).

TABLE 6 Compliance classification for the ITT population by treatment and control

Classification	Treatment[a] *n* = 74	Control[b] *n* = 74	Total *N* = 148	*p*-value
Non-complier	34 (45.9%)	28 (37.8%)	62 (41.9%)	0.32[c]
Complier[d]	40 (54.1%)	46 (62.2%)	86 (58.1%)	

a Treatment group includes BMT + NMES and BMT + SET + NMES.
b Control group includes BMT and BMT + SET.
c *P*-values for the difference between groups were computed using Pearson's chi-squared test.
d Patients are defined as a complier if they are compliant for all their assigned treatments [75% EA, 50% SET and 50% device (NMES)].

Table 7 shows the descriptive statistics for the AWD by treatment versus control by follow-up periods. At baseline there were 92 patients in the treatment group and 98 in the control group. The means (SD) in AWD based on data recorded for the treatment and control at baseline were 242.97 (187.08) m and 220.12 (148.27) m. At 3 months the number of patients in the treatment group was down to 80, but the mean AWD was up to 370.38 (251.38) m. The control group was likewise down to 80 patients, while the mean AWD was up to 327.74 (222.65) m.

A Tobit regression model was used to incorporate the right-censored data and estimate the difference in the distance walked between the treatment (NMES + BMT and NMES + BMT + SET) and control (BMT and BMT + SET) at 3 months. The model includes the AWD baseline measurement, a treatment indicator and the type of centre (SET vs. non-SET) as covariates (see *Table 8*).

The results of the Tobit regression models for both the raw data of AWD (Model 1) and the transformed square root of the AWD (Model 2) are found in *Table 8* (see also *Report Supplementary Material 3*, *Table 1 for PP population results*). Model 1 indicates that the difference in AWD between treatment (device) and control (no device) at 3 months is expected to be 27.18 m (95% CI −26.92 to 81.28; $p = 0.323$). Similarly,

TABLE 7 Summary statistics of AWD by visit and treatment for the complete cases in the ITT population

Visit	Treatment	*N*	Mean[a]	SD[a]	Median	Min	Max
Baseline							
	Treatment[b]	92	242.97	187.08	183.38	10.00	756.39
	Control[c]	98	220.12	148.27	164.00	1.27	720.00
	Difference		**22.86**				
3 months							
	Treatment	80	370.38	251.38	300.00	0.05	790.00
	Control	80	327.74	222.65	276.62	1.50	790.00
	Difference		**42.63**				
6 months							
	Treatment	69	393.60	260.41	356.00	16.09	790.00
	Control	66	359.25	234.07	290.00	30.00	790.00
	Difference		**34.35**				
12 months							
	Treatment	47	443.83	321.47	300.00	40.94	790.00
	Control	62	386.50	267.05	313.59	32.19	790.00
	Difference		**57.34**				

a Mean and SD were calculated using a Tobit model for censored data.
b Treatment group includes BMT + NMES and BMT + SET + NMES.
c Control group includes BMT and BMT + SET.

TABLE 8 Output of the right-censored Tobit regression model for AWD at 3 months for the complete case in the ITT population (*N* = 160)

	Tobit regression (AWD raw data)	Tobit regression (AWD square root transformation)
Independent variables	**Model 1 Coefficient (95% CI) *p*-value**	**Model 2 Coefficient (95% CI) *p*-value**
AWD at baseline	0.87 (0.71 to 1.03) $p \leq 0.001$	0.78 (0.65 to 0.92) $p \leq 0.001$
Treatment[a]		
Control: BMT and BMT + SET	–	–
Treatment: NMES + BMT and NMES + BMT + SET	27.18 (−26.92 to 81.28) $p = 0.323$	0.83 (−0.67 to 2.34) $p = 0.28$
Type of centre[b]		
Non-SET	–	–
SET	121.71 (67.32 to 176.10) $p \leq 0.001$	3.29 (1.77 to 4.82) $p \leq 0.001$
Constant	58.87 (−3.35 to 121.09) $p = 0.064$	4.05 (1.62 to 6.48) $p \leq 0.001$

a Control: local available exercise therapy (BMT and BMT + SET) as reference category.
b Non-SET exercise centres as reference category.

Notes
Model 1: Tobit regression model (AWD at 3 months) = intercept + AWD (baseline) + treatment + type of centre.
Model 2: Tobit regression model (square root of AWD at 3 months) = intercept + square root of AWD (baseline) + treatment + type of centre.

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the result of Model 2 indicates the square root of AWD difference at 3 months to be 0.835 units higher (95% CI −0.67 to 2.34; $p = 0.276$). These findings are not statistically significant for either model at a significance level of 5%; however, the findings suggest that NMES may be beneficial at improving AWD when used as an adjunct to standard care.

For SET versus non-SET, both Model 1 and Model 2 indicate a significant difference. Model 1 indicates that we would expect the AWD at 3 months to be 121.1 m higher (95% CI 67.32 to 176.10; $p < 0.001$) for patients from a SET centre compared with a patient from a non-SET centre. Similar results are observed in Model 2 for the transformed square root of the AWD at 3 months being 3.29 units higher (95% CI 1.77 to 4.82; $p < 0.001$).

The per-protocol analysis showed similar results (see *Report Supplementary Material 3*, *Table 1*).

A chi-squared test was performed to examine if there was a difference between treatment and control when an improvement of more than 60 m from baseline to 3 months was observed (see *Report Supplementary Material 3*, *Table 2*). The table shows that 46 patients (57.5%) showed an improvement of more than 60 m in AWD at 3 months in the treatment arm, while 36 patients (45.0%) showed the same improvement in the control arm. However, there was no statistically significant difference in the proportions of improvement between treatment and control as the difference was 12.5% with a 95% CI of −2.9 to 27.9%; $p = 0.11$. For improvement of more than 100 m, we also observed no statistically significant difference between treatment arms: 7.5% with a 95% CI of −7.7 to 22.7.%; $p = 0.335$.

A multilevel Tobit model (see *Report Supplementary Material 3*, *Table 3*) for right-censored data was used to investigate the difference in AWD between the two treatment groups at 3, 6 and 12 months adjusting for AWD baseline measurement, treatment, time, time × treatment interaction, type of centre (SET vs. non-SET), age, gender, BMI and smoking status as fixed effects and patient as a random effect.

The multilevel model shows that the square root of AWD at baseline, type of centre (SET vs. non-SET) and gender had a statistical significance at a 5% level, for both the multilevel model with the raw data and with the square-root transformation.

The multilevel Tobit model for AWD indicates that we expect a decreasing trend of AWD over time for the treatment arm in comparison to the control arm. That is, we observed a decrease at 6 months of 10.42 m (95% CI −64.07 to 43.23; $p = 0.70$) for Model 1 using raw data or −0.23 units (95% CI −1.65 to 1.2; $p = 0.76$) for Model 2 using the square-root transformation. Further, we observed a decrease at 12 months of −27.69 m (95% CI −86.76 to 31.38; $p = 0.36$) in Model 1 using raw data or −0.65 units (95% CI −2.21 to 0.92; $p = 0.42$) in Model 2 using the square-root transformation.

We observed an increase of 32.82 m (95% CI −27.29 to 92.94; $p = 0.29$) raw AWD data or 0.88 units (95% CI −0.75 to 2.51; $p = 0.29$) for the square-root transformation of AWD in the treatment arm in comparison to the control arm, while for type of centre (SET vs. non-SET) we observed an increase of 129.6 m (95% CI 74.6 to 184.6; $p < 0.001$) raw AWD data or 3.39 units (95% CI −0.75 to 2.51; $p = 0.29$) for the square-root transformation of AWD for a patient from a SET centre compared with a patient from a non-SET centre.

When the Tobit regression model was adjusted by centre (see *Report Supplementary Material 3*, *Table 4*), we found that only AWD at baseline showed a statistically significant difference between arms for Model 1 and Model 2. For the multilevel Tobit model (see *Report Supplementary Material 3*, *Table 5*), we found that both AWD at baseline and gender showed a statistically significant difference between treatments for both Model 1 and Model 2. Outputs of the results using multiple imputation are also presented in the *Report Supplementary Material 3*, *Tables 6* and *7*.

An additional analysis using ANCOVA with bootstrap was performed (see *Report Supplementary Material 3*, *Tables 8* and *9*).

From *Table 7* we observe that the mean difference of the AWD between the treatment and control arm is 22.86 at baseline and 42.63 at 3 months. After adjusting for this difference, an ANCOVA linear regression model showed that these differences were not significant, with a difference between the treatment groups of 20.75 (95% CI −30.32 to 71.81; $F(1,156) = 0.64$, $p = 0.424$).

We notice that the results of the ANCOVA confirm the finding in the Tobit regression models both for raw data and for the transformed squared root: that the difference in the AWD between treatment arm and control arm is not significant at 3 months.

Secondary outcomes

Initial claudication distance

Table 9 shows the descriptive statistics of the ICD by treatment versus control. At baseline, there were 92 patients in the treatment arm and 98 patients in the control arm with ICD information. The mean (SD) of the ICD is 105.79 (106.27) m for the treatment group and 99.10 (77.06) m for the control group. At 3 months the mean (SD) of ICD had risen to 211.45 (181.83) m for the treatment group and 179.73 (147.03) m for the control group.

The result of the multilevel models (Model 1 and Model 2) for ICD (see *Table 10*) shows ICD at baseline, type of centre (SET vs. not-SET) and gender had statistically significant differences at a 5% level. See also *Report Supplementary Material 3*, *Table 10* for PP population results.

TABLE 9 Summary statistics of the ICD by visit and treatment for the complete cases in the ITT population

Visit	Treatment	*N*	Mean[a]	SD[a]	Median	Min	Max
Baseline							
	Treatment[b]	92	105.79	106.27	78.27	5.00	659.83
	Control[c]	98	99.10	77.06	79.60	1.18	386.24
	Difference		**6.69**				
3 months							
	Treatment	80	211.45	181.83	155.46	0.05	790.00
	Control	80	179.73	147.03	144.84	1.50	790.00
	Difference		**31.72**				
6 months							
	Treatment	69	233.57	191.11	193.12	3.00	790.00
	Control	67	201.81	139.40	176.22	16.09	790.00
	Difference		**31.77**				
12 months							
	Treatment	47	297.50	270.41	193.12	20.47	790.00
	Control	63	239.06	200.31	180.00	16.09	790.00
	Difference		**58.45**				

a Mean and SD were calculated using a Tobit model for censored data.
b Treatment group includes BMT + NMES and BMT + SET + NMES.
c Control group includes BMT and BMT + SET.

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TABLE 10 Output of the right-censored multilevel Tobit model to assess the effects of baseline characteristics for ICD at 3, 6 and 12 months for the complete cases of the ITT population (*N* = 159)

	Multilevel Tobit model (ICD raw data)	Multilevel Tobit model (ICD square-root transformation)
	Model 1 Coefficient (95% CI) *p*-value	**Model 2 Coefficient (95% CI) *p*-value**
ICD at baseline	0.72 (0.5 to 0.95) $p <$ **0.001**	0.64 (0.47 to 0.81) $p <$ **0.001**
Treatment[a]		
Control[b]		
Treatment[c]	34.43 (−16.12 to 84.99) $p = 0.18$	0.97 (−0.6 to 2.55) $p = 0.23$
Time[d]		
Month 3		
Month 6	20.29 (−14.79 to 55.37) $p = 0.26$	0.83 (−0.23 to 1.88) $p = 0.12$
Month 12	56.06 (20.15 to 91.97) $p <$ **0.001**	1.79 (0.71 to 2.86) $p <$ **0.001**
Treatment × time[e]		
Treatment: NMES + BMT and NMES + BMT + SET × month 6	−7.31 (−56.46 to 41.84) $p = 0.77$	−0.41 (−1.89 to 1.06) $p = 0.58$
Treatment: NMES + BMT and NMES + BMT + SET × month 12	−3.77 (−57.46 to 49.92) $p = 0.89$	−0.4 (−2.02 to 1.21) $p = 0.63$
Type of centre[f]		
Non-SET		
SET	80.87 (35.56 to 126.17) $p <$ **0.001**	2.33 (0.91 to 3.76) $p <$ **0.001**
Age (years)	0.26 (−2.37 to 2.88) $p = 0.85$	0.01 (−0.07 to 0.09) $p = 0.84$
Gender[g]		
Female		
Male	−49.12 (−100.08 to 1.84) $p = 0.06$	−1.83 (−3.45 to −0.22) $p =$ **0.03**
BMI (kg/m^2)	1.93 (−1.77 to 5.63) $p = 0.31$	0.03 (−0.09 to 0.14) $p = 0.65$
Smoking[h]		
Never		
Current smoker	13.06 (−88.01 to 114.14) $p = 0.8$	−0.22 (−3.4 to 2.97) $p = 0.89$
Former smoker	42.36 (−51.15 to 135.87) $p = 0.38$	1.09 (−1.86 to 4.03) $p = 0.47$
Constant	−11.57 (−272.38 to 249.24) $p = 0.93$	4.43 (−4.03 to 12.89) $p = 0.31$

a Control: local available exercise therapy (EA and EA + SET) as a reference category.
b Control group includes BMT and BMT + SET.
c Treatment group includes BMT + NMES and BMT + SET + NMES.
d Month 3 as a reference category.
e Control and Month 3 as the reference category for the interaction term (treatment and time).
f Non-SET exercise centres as reference category.
g Female as reference category.
h Never smoked as reference standard.

Notes
Model 1: multilevel Tobit model of the ICD (3, 6 and 12 months) = intercept + ICD (baseline) + treatment + time + interaction of treatment and time + type of centre + age + gender + BMI + smoking status.
Model 2: multilevel Tobit model of the square root of ICD (3, 6 and 12 months) = intercept + square root of ICD (baseline) + treatment + time + interaction of treatment and time + type of centre + age + gender + BMI + smoking status.

Model 1 indicates that we would expect the average of the ICD at a given point to be 34.43 m (95% CI −16.12 to 84.99; $p = 0.18$) higher for the treatment arm than the control. Model 2 indicates the average of the square root of the ICD to be 0.97 units (95% CI −0.6 to 2.55; $p = 0.26$) higher for the treatment arm.

For Model 1 for patients in the SET centre, we expect the average of the ICD to be 80.87 m (95% CI 35.56 to 126.17; $p < 0.001$) in comparison with patients from the non-SET centres. For Model 2 we would expect the average of the square root of the ICD to be 2.33 units (95% CI 0.91 to 3.76; $p < 0.001$) higher for patients in a SET centre compared with a patient from a non-SET centre. Each model shows a statistically significant difference.

Model 1 also estimates that male patients will reduce the ICD by 49.12 m (95% CI −100.08 to 1.84; $p = 0.06$) in comparison with female patients. For the interaction term of treatment × time, both Model 1 and Model 2 indicate that there was a reduction in metres in ICD between treatment and control over the 12-month follow-up period.

The multilevel Tobit model for ICD indicates that we expect a decrease in metres of ICD over time for the treatment arm in comparison to the control. That is, we observed a decrease in the treatment arm in comparison to the control at 6 months of 7.31 m (95% CI −56.46 to 41.84; $p = 0.77$) for Model 1 using raw data or −0.41 units (95% CI −1.89 to 1.06; $p = 0.58$) for Model 2 using the square-root transformation. Likewise, we observed a decrease at 12 months of −3.77 m (95% CI −57.46 to 49.92; $p = 0.89$) for Model 1 using raw data or −0.4 units (95% CI −2.02 to 1.21; $p = 0.63$) for Model 2 using the square-root transformation.

A chi-squared test was performed to examine if there was a difference between treatment and control when an improvement of more than 60 m from baseline to 3 months was observed.

From *Report Supplementary Material 3*, *Table 11* we can see that 41 patients (51.2%) showed an improvement of more than 60 m in ICD at 3 months in the treatment arm, while 30 patients (37.5%) showed the same improvement in the control arm. There was no statistically significant difference in the proportions of improvement between treatment and control as the difference was 13.7% with a 95% CI of −1.5 to 29.0%; $p = 0.08$. The same pattern was observed when an improvement of more than 100 m was tested.

See also *Report Supplementary Material 3*, *Table 12* for ICD analysis using centres as covariate and *Report Supplementary Material 3*, *Tables 13* and *14* for using multiple imputation for ICD.

Haemodynamic assessments

Duplex ultrasonography

Analysis for Duplex ultrasonography is composed of two measurements: VF and TAMV.

Table 11 shows the descriptive statistics of VF by treatment versus control. At baseline, there were 80 patients in the treatment arm and 87 patients in the control arm with VF measurements available. The mean (SD) of VF was 300.06 (155.10) for the treatment group and 296.89 (198.40) for the control group. At 3 months there were 71 patients with VF measurements available. The mean (SD) went down to 296.77 (146.30) for the treatment group and to 280.96 (179.03) for the control group.

The VF regression in Model 1 shows that there was not a significant difference between treatment arms but we expected an increase in VF at 3 months of 15.61 cc/minute (95% CI −36.89 to 68.11; $p = 0.56$) in the treatment arm, while in Model 2 we found that the square root of VF at 3 months increased by 0.48 units (95% CI −0.98 to 1.95; $p = 0.52$) in the treatment arm. For the centre (SET vs. non-SET) we

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TABLE 11 Summary of duplex ultrasonography (VF[a] – measured in one leg) for the ITT population by time and treatment

Time	Treatment	*N*	Mean	SD	Median	Min	Max
Baseline	Treatment[b]	80	300.06	155.10	269.60	28.40	795.40
	Control[c]	87	296.89	198.40	266.00	2.00	983.00
3 months	Treatment	71	296.77	146.30	282.80	8.80	707.00
	Control	71	280.96	179.03	234.00	29.00	864.00

a Average of five readings taken from VF (measured in one leg) by patient in the device group.
b Treatment group includes BMT + NMES and BMT + SET + NMES.
c Control group includes BMT and BMT + SET.

TABLE 12 Output of linear regression model for duplex ultrasonography (VF – measured in one leg) at 3 months for the complete cases of the ITT population (*N* = 135)

	Linear regression model (VF raw data)	Linear regression model (VF squar-root transformation)
	Model 1 **Coefficient (95% CI) *p*-value**	**Model 2** **Coefficient (95% CI) *p*-value**
VF at baseline (cc/minute)	0.3 (0.15 to 0.45) ***p* < 0.001**	0.39 (0.25 to 0.53) ***p* < 0.001**
Treatment[a]		
Control[b]		
Treatment[c]	15.61 (−36.89 to 68.11) *p* = 0.56	0.48 (−0.98 to 1.95) *p* = 0.52
Type of centre[d]		
Non-SET		
SET	52.57 (−3.12 to 108.25) *p* = 0.06	1.17 (−0.4 to 2.74) *p* = 0.14
Age (years)	−0.96 (−3.83 to 1.91) *p* = 0.51	−0.04 (−0.12 to 0.04) *p* = 0.38
Gender[e]		
Female		
Male	35.08 (−24.75 to 94.92) *p* = 0.25	0.62 (−1.05 to 2.29) *p* = 0.47
BMI (kg/m^2)	2.76 (−1.57 to 7.09) *p* = 0.21	0.06 (−0.06 to 0.18) *p* = 0.35
Constant	127.36 (−120.39 to 375.11) *p* = 0.31	9.44 (2.37 to 16.51) *p* = 0.01

a Control: local available exercise therapy (BMT and BMT + SET) as reference category.
b Control group includes BMT and BMT + SET.
c Treatment group includes BMT + NMES and BMT + SET + NMES.
d Non-SET exercise centres as reference category.
e Female as reference category.

Notes
Model 1: linear regression model of VF = intercept + VF (baseline) + treatment + type of centre + age + gender + BMI.
Model 2: linear regression model of the square root of VF = intercept + square root of VF (baseline) + treatment + type of centre + age + gender + BMI.

observed an increase in VF at 3 months of 52.57 cc/minute (95% CI −36.89 to 68.11; *p* = 0.56) for a patient in a SET centre compared with a patient from a non-SET centre using Model 1, while for Model 2 we found that the square root of VF at 3 months would increase by 1.17 units (95% CI −0.40 to 2.74; *p* = 0.14) in a SET centre (see *Table 12*). See also *Report Supplementary Material 3*, *Table 15* for PP population results.

TABLE 13 Output of linear regression model for duplex ultrasonography (TAMV – measured in one leg) at 3 months for the complete cases of the ITT population (*N* = 139)

	Linear regression model (TAMV raw data)	Linear regression model (TAMV square-root transformation)
	Model 1 **Coefficient (95% CI) *p*-value**	**Model 2** **Coefficient (95% CI) *p*-value**
TAMV at baseline (cm/second)	0.47 (0.33 to 0.61) ***p* < 0.001**	0.48 (0.35 to 0.62) ***p* < 0.001**
Treatment[a]		
Control[b]		
Treatment[c]	0.32 (−1.26 to 1.89) *p* = 0.69	0.07 (−0.16 to 0.3) *p* = 0.56
Type of centre[d]		
Non-SET		
SET	1.71 (0.06 to 3.35) ***p* = 0.04**	0.25 (0.01 to 0.49) ***p* = 0.04**
Age (years)	0.03 (−0.06 to 0.11) *p* = 0.52	0 (−0.01 to 0.02) *p* = 0.53
Gender[e]		
Female		
Male	−1.39 (−3.16 to 0.38) *p* = 0.12	−0.21 (−0.47 to 0.05) *p* = 0.11
BMI (kg/m²)	−0.04 (−0.17 to 0.09) *p* = 0.54	−0.01 (−0.03 to 0.01) *p* = 0.45
Constant	5.73 (−1.81 to 13.28) *p* = 0.14	1.71 (0.54 to 2.88) *p* = 0.01

a Control: local available exercise therapy (BMT and BMT + SET) as reference category.
b Control group includes BMT and BMT + SET.
c Treatment group includes BMT + NMES and BMT + SET + NMES.
d Non-SET exercise centres as reference category.
e Female as reference category.

Notes
Model 1: linear regression model: TAMV measured in one leg at 3 months = intercept + TAMV (baseline) + treatment + type of centre + age + gender + BMI.
Model 2: linear regression model: square root of TAMV measured in one leg at 3 months = intercept + square root of TAMV (baseline) + treatment + type of centre + age + gender + BMI.

TABLE 14 Summary of the log LDF (blood flux[a] – measured in one leg) for the ITT population by time and treatment

		N	Mean	SD	Median	Min	Max
Baseline	Treatment[b]	90	2.61	0.58	2.57	1.27	3.93
	Control[c]	96	2.38	0.56	2.28	1.22	3.88
3 months	Treatment	76	2.79	0.69	2.82	1.32	4.09
	Control	77	2.30	0.65	2.26	−0.11	3.91
6 months	Treatment	70	2.49	0.57	2.44	1.50	3.66
	Control	66	2.50	0.62	2.41	1.48	3.91
12 months	Treatment	51	2.64	0.61	2.66	1.19	4.05
	Control	63	2.53	0.56	2.52	1.31	4.07
Total	Treatment	287	2.63	0.62	2.62	1.19	4.09
	Control	302	2.41	0.60	2.38	−0.11	4.07

a Average of five readings taken from VF (measured in one leg) by patient in the device group.
b Treatment group includes BMT + NMES and BMT + SET + NMES.
c Control group includes BMT and BMT + SET.

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TABLE 15 Output of ANCOVA model for the LDF (blood flux – measured in one leg) between baseline and follow-up periods (3, 6 and 12 months) for the ITT population

Source	Partial SS	df	MS	*F*	Prob>*F*
Model	130.99	191.00	0.69	2.87	**0.000**
Log blood flux at baseline	1.24	1.00	1.24	5.17	0.024
Treatment	0.24	1.00	0.24	0.99	**0.321**
Time	0.63	3.00	0.21	0.87	0.455
Treatment × time	3.88	3.00	1.29	5.4	**0.001**
Subject	55.41	183.00	0.30	**1.27**	0.029
Residual	94.25	394.00	0.24		
R^2 = 0.5816	Adjusted R^2 = 0.38			Root MSE = 0.49	

MS, mean square; MSE, mean squared error; SS, sum of square.

Note
Repeated-measurement ANCOVA model: log LDF – blood flux in one leg at 3, 6, 12 months = intercept + treatment group indicator + log blood flux (baseline) + time + treatment × time + subject.

Regression models for TAMV (see *Table 13*) show that both the TAMV at baseline and the type of centre are statistically significant at a 5% level. The TAMV regression in Model 1 shows that there was not a significant difference between treatment arms but we observed an increase in TAMV at 3 months of 0.32 cm/s (95% CI −1.26 to 1.89; $p = 0.69$) in the treatment arm. While using Model 2, we found that the square root of TAMV at 3 months would increase by 0.07 units (95% CI −0.16 to 0.03; $p = 0.56$). For the centre (SET vs. non-SET), when using Model 1, we would expect an increase in TAMV at 3 months of 1.71 cm/s (95% CI 0.06 to 3.35; $p = 0.04$) for a patient in a SET centre compared with a patient from a non-SET centre. While using Model 2, we observed that the square root of TAMV at 3 months increased by 0.07 units (95% CI −0.16 to 0.03; $p = 0.56$) in a SET centre. See also *Report Supplementary Material 3*, *Table 16* for PP population results.

Laser doppler flowmetry

Table 14 shows the summary statistics for LDF by treatment versus control for the ITT population. The measurements were collected at baseline, 3, 6 and 12 months. At baseline, there were 90 patients in the treatment arm and 96 patients in the control arm with LDF measurements, while at 12 months there were 51 and 63 patients, respectively. The baseline mean (SD) of the log LDF for the treatment arm was 2.61 (0.58) at baseline, while for the control arm it was 2.38 (0.56). At 12 months the mean (SD) of the log LDF was 2.64 (0.61) for the treatment arm and 2.53 (0.56) for the control arm. A table showing the raw LDF data summary statistics can be seen in *Report Supplementary Material 3*, *Table 17*.

The total LDF we observed for the log mean of blood flux was 2.63 (0.62) for the treatment arm and 2.41 (0.60) for the control arm. After adjusting for this difference, an ANCOVA linear regression model (see *Table 15*) showed that these differences were not significant, with a difference between the treatment groups of −0.54 (95% CI −1.7 to 0.061; $F(1,394) = 0.99$, $p = 0.321$). See also *Report Supplementary Material 3*, *Table 18* for underlying coefficients.

For the interaction term of treatment × time, the ANCOVA indicated that there was a difference in the log blood flux between treatment and control over the 12-month follow-up period $F(3,394) = 5.4$, $p < 0.001$. Particularly the results indicate that we expect a decrease in the log blood flux over time for the treatment arm in comparison to the control arm. That is, we expected a difference of 0.2 log of blood flux (95% CI −0.02 to 0.42; $p < 0.07$) at 3 months, a difference of −0.27 log of blood flux (95% CI −0.5 to −0.04; $p = 0.02$) at 6 months, and a difference of −0.09 log of blood flux (95% CI −0.34 to

TABLE 16 Summary of ABPI (measured in one leg) for the ITT population by time and treatment

Visit	Treatment	*N*	Mean	SD	Median	Min	Max
Baseline							
	Treatment[a]	90	0.72	0.18	0.70	0.30	1.20
	Control[b]	96	0.76	0.21	0.70	0.40	1.30
3 months							
	Treatment	81	0.72	0.21	0.70	0.30	1.30
	Control	79	0.74	0.23	0.80	0.20	1.30
6 months							
	Treatment	72	0.74	0.20	0.70	0.40	1.40
	Control	66	0.77	0.22	0.75	0.30	1.30
12 months							
	Treatment	53	0.74	0.22	0.80	0.30	1.20
	Control	66	0.79	0.23	0.80	0.20	1.30

a Treatment group includes BMT + NMES and BMT + SET + NMES.
b Control group includes BMT and BMT + SET.

TABLE 17 Output of linear mixed models for the transformed log right and left ABPI between baseline and follow-up periods (3, 6 and 12 months) for the complete-cases ITT population (*N* = 159)

	Log-right ABPI	Log-left ABPI
	Coefficient (95% CI) *p*-value	**Coefficient (95% CI) *p*-value**
Log ABPI at baseline	0.82 (0.71 to 0.93) ***p* < 0.001**	0.75 (0.66 to 0.83) ***p* < 0.001**
Treatment[a]		
Control: BMT and BMT + SET		
Treatment: NMES + BMT and NMES + BMT + SET	0.05 (−0.02 to 0.12) *p* = 0.17	−0.03 (−0.1 to 0.03) *p* = 0.32
Time[b]		
Month 3		
Month 6	0.07 (0.02 to 0.12) ***p* = 0.01**	0 (−0.06 to 0.07) *p* = 0.93
Month 12	0.07 (0.02 to 0.13) ***p* = 0.01**	−0.02 (−0.08 to 0.05) *p* = 0.59
Treatment × time[c]		
Treatment: NMES + BMT and NMES + BMT + SET × month 6	−0.04 (−0.11 to 0.04) *p* = 0.34	0.01 (−0.08 to 0.1) *p* = 0.78
Treatment: NMES + BMT and NMES + BMT + SET × month 12	−0.06 (−0.13 to 0.02) *p* = 0.16	0.03 (−0.06 to 0.13) *p* = 0.49
Constant	−0.12 (−0.18 to −0.06) *p* < 0.001	−0.05 (−0.12 to 0.01) *p* = 0.11

a Control: local available exercise therapy (BMT and BMT + SET) as reference category.
b Three months as reference category.
c Control and 3 months as reference category for the interaction term (treatment and time).

Note
Mixed models adjusted for log right or left ABPI at baseline, with time, treatment, and interaction term time and treatment as fixed effects and patient as random effect.

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TABLE 18 Summary of disease-specific and generic patient-reported quality-of-life outcomes[a]

Outcome	Treatment[b]		Control[c]		Between-group
	No. of patients	Score	No. of patients	Score	Difference in score (95% CI)[d]
ICQ health scale[e]					
Baseline	90	41.98 ± 13.26	94	45.92 ± 13.09	
3 months	84	36.55 ± 13.86	82	41.33 ± 14.52	−1 (−4.5 to 2.4) p = 0.56
6 months	78	35.20 ± 15.07	77	39.27 ± 14.51	−0.1 (−3.7 to 3.4) p = 0.94
12 months	76	36.99 ± 17.38	76	36.21 ± 16.45	4.3 (0.7 to 7.9) p **= 0.02**
EQ-5D-5L health scale[f]					
Baseline	91	69.73 ± 18.03	97	69.61 ± 17.69	
3 months	85	74.02 ± 15.13	84	66.11 ± 21.09	7.1 (1.8 to 12.4) p **= 0.01**
6 months	79	73.13 ± 19.32	77	68.36 ± 20.85	3.5 (−1.9 to 8.9) p = 0.21
12 months	77	70.40 ± 20.98	76	68.03 ± 19.61	1.9 (−3.5 to 7.4) p = 0.49
EQ-5D-5L health index[g]					
Baseline	91	0.63 ± 0.20	97	0.62 ± 0.20	
3 months	85	0.66 ± 0.20	84	0.62 ± 0.21	0.04 (−0.02 to 0.09) p = 0.17
6 months	79	0.65 ± 0.22	78	0.66 ± 0.18	−0.02 (−0.07 to 0.04) p = 0.56
12 months	77	0.65 ± 0.26	76	0.66 ± 0.20	0.002 (−0.05 to 0.05) p = 0.94
SF-36 Physical – component summary[h]					
Baseline	91	35.71 ± 8.22	95	36.14 ± 7.90	
3 months	84	38.80 ± 8.87	84	37.42 ± 8.48	1.7 (−0.6 to 4) p = 0.14
6 months	79	39.47 ± 9.74	77	37.62 ± 9.85	2.3 (0.02 to 4.7) p = 0.048
12 months	76	38.16 ± 9.98	75	39.46 ± 9.40	−0.6 (−3 to 1.7) p = 0.6
SF-36 Mental – component summary[h]					
Baseline	91	52.06 ± 11.61	95	49.75 ± 12.47	
3 months	84	52.99 ± 10.05	84	48.24 ± 13.15	2.1 (−0.9 to 5.1) p = 0.18
6 months	79	52.79 ± 10.73	77	49.09 ± 10.90	1.3 (−1.8 to 4.3) p = 0.43
12 months	76	52.62 ± 11.68	75	48.90 ± 12.24	1.5 (−1.6 to 4.6) p = 0.34

a Plus–minus values are means ±SD.
b Treatment group includes BMT + NMES and BMT + SET + NMES.
c Control group includes BMT and BMT + SET.
d The between-group differences were estimated by a mixed model adjusted for each baseline QoL score and time as fixed effects and centre and patients as random effects. The control group was the reference group. The widths of the CIs were not adjusted for multiple comparisons and should not be used for formal reference.
e Scores on the ICQ range from 0 to 100, with higher scores indicating worse health related to IC.
f Scores on the EuroQol Group 5-Dimension 5-Level questionnaire (EQ-5D-5L) health scale (a visual-analogue scale) range from 0 to 100, with higher scores indicating better health.
g Score on the EQ-5D-5L health index range from 0 to 1, with higher scores indicating better health. The EQ-5D-5L health index was calculated with the value set for England.[29]
h Scores on the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) Physical Component Summary and Mental Component Summary range from 1 to 100, with higher scores indicating better QoL.

TABLE 19 Summary table of device use questionnaire

Questions	Value *N* = 88
Ease of use	
1 – Very easy	77 (87.5%)
2	6 (6.8%)
3	1 (1.1%)
4	0 (0.00%)
5 – Very difficult	0 (0.00%)
Missing (number of patients), *N* (%)	4 (4.5%)
Reduces leg pain	
1 – Yes, a lot	14 (15.9%)
2	22 (25.0%)
3	26 (29.5%)
4	11 (12.5%)
5 – Not at all	11 (12.5%)
Missing (number of patients), *N* (%)	4 (4.5%)
Increased walk distance	
No	8 (9.1%)
No change	19 (21.6%)
Yes	57 (64.8%)
Missing (number of patients), *N* (%)	4 (4.5%)
Used as instructed	
No, why	2 (2.3%)
Yes	82 (93.2%)
Missing (number of patients), *N* (%)	4 (4.5%)
Could have used more	
No	28 (31.8%)
Yes	56 (63.6%)
Missing (number of patients), *N* (%)	4 (4.5%)
Used after treatment	
1 – Yes, a lot	51 (58.0%)
2	13 (14.8%)
3	16 (18.2%)
4	0 (0.0%)
5 – Not at all	4 (4.5%)
Missing (number of patients), *N* (%)	4 (4.5%)

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0.15; p = 0.46) at 12 months in the treatment arm in comparison to the control arm (see also *Report Supplementary Material 3*, *Table 19*).

Ankle–brachial pressure index

Table 16 shows the descriptive statistics for ABPI within the ITT population by treatment versus control. At baseline, there were 90 patients in the treatment arm and 96 patients in the control arm with ABPI measurements, while at 12 months there were 53 and 66 patients, respectively. At baseline, the mean (SD) ABPI for the treatment arm was 0.72 (0.18) while for the control arm the mean ABPI was 0.76 (0.21). At 12 months, the mean ABPI for both arms had gone up; 0.74 (0.22) for the treatment arm and 0.79 (0.23) for the control arm.

Participants' log-right ABPI significantly increased over the follow-up period, irrespective of treatment group, by 0.07 (95% CI 0.02 to 0.12, p = 0.01) at 6 months and by 0.07 (95% CI 0.02 to 0.13, p = 0.01) at 12 months (see *Table 17*). However, there were no significant findings between the treatment group and the control group nor any significant findings for log-left ABPI (see *Table 17*). See also *Report Supplementary Material 3*, *Table 20* for PP population results.

Quality of life

Quality-of-life outcomes are summarised in *Table 18*, see *Report Supplementary Material 3*, *Table 21* (SF-36 domain scores) and see *Report Supplementary Material 3*, *Figures 1–4*. There were no clear differences in EQ-5D-5L or SF-36 scores between the treatment groups over the 12-month follow-up period, although there was a significant difference in the EQ-5D-5L health scale following the 3-month treatment period, indicating a better health score in the device group compared with the control group (7.1; 95% CI 1.8 to 12.4; p = 0.01), but this was not sustained at 6 or 12 months. Disease-specific ICQ scores decreased in both groups, indicating less pain from baseline throughout the follow-up period. Within-group analysis showed a significant decrease in ICQ score from baseline to 12 months in the control arm in comparison with the device arm (4.3; 95% CI 0.7 to 7.9; p = 0.02), as shown in *Table 18*.

The significance of the p values needs to be interpreted with caution as we did not control for multiple testing.

Compliance with interventions

For each of the treatment groups compliance was defined as follows:

- EA (part of BMT): compliant if completed 75% or more of recommended level of EA (75% of minutes performing exercises recommended by centre).
- SET: compliant if attended 50% or more SET sessions held by centre.
- NMES: compliant if completed 75% or more of recommended level of NMES usage.

Compliance was measured for each of EA, SET and NMES separately to determine the complier/non-complier classification.

Compliance to EA was 52.1% (non-compliance 27.4%).

Compliance to SET was 69.7% (non-compliance 19.2%).

Compliance to NMES was 73.9% (non-compliance 13.0%).

Device experience questionnaire

The results of the device use questionnaire can be found in *Table 19*. Of the 88 device respondents, 87.5% stated that the device was 'very easy' to use, and the majority (64.8%) believed the device increased their walking distance; 63.6% stated that they could have used the device more frequently, with 58.0% using the device 'a lot' following the 3-month treatment period.

TABLE 20 Output of right-censored Tobit regression models for AWD at 3 months to assess the effects of each subgroup for the complete cases in the ITT population

	Tobit regression (AWD raw data) Model 1[a]		Tobit regression (AWD square-root transformation) Model 2[b]	
Independent variables	**Coefficient (95% CI)**	***p*-value**	**Coefficient (95% CI)**	***p*-value**
AWD at baseline	0.87 (0.72 to 1.03)	***p* < 0.001**	0.79 (0.65 to 0.93)	***p* < 0.001**
Subgroup 1				
Non-SET[c]	–	–	–	–
SET	80.56 (3.56 to 157.56)	***p* = 0.04**	2.36 (0.21 to 4.51)	***p* = 0.03**
Treatment				
Control: BMT and BMT + SET[c]				
Treatment: NMES + BMT and NMES + BMT + SET	−18.01 (−98.81 to 62.78)	*p* = 0.66	−0.19 (−2.45 to 2.06)	*p* = 0.87
Treatment × subgroup 1				
Control × non-SET[c]				
Treatment × SET	80.98 (−27.16 to 189.12)	*p* = 0.13	1.85 (−1.18 to 4.88)	*p* = 0.23
Constant	83.33 (13.39 to 153.27)	*p* = 0.02	4.57 (2.00 to 7.13)	***p* < 0.001**
AWD at baseline	1.01 (0.76 to 1.26)	***p* < 0.001**	0.87 (0.66 to 1.07)	***p* < 0.001**
Subgroup 2				
BMT + SET[c]	–	–	–	–
BMT + SET + NMES	64.26 (−20.03 to 148.54)	*p* = 0.13	1.72 (−0.56 to 4.01)	*p* = 0.14
Constant	135.63 (57.28 to 213.98)	***p* < 0.001**	5.88 (2.67 to 9.08)	***p* < 0.001**
AWD at baseline	0.74 (0.55 to 0.92)	***p* < 0.001**	0.7 (0.52 to 0.88)	***p* < 0.001**
Subgroup 3				
BMT[c]	–	–	–	–
BMT + NMES	−12.75 (−76.42 to 50.91)	*p* = 0.69	−0.09 (−2.01 to 1.83)	*p* = 0.93
Constant	114.18 (51.08 to 177.28)	***p* < 0.001**	5.85 (2.92 to 8.78)	***p* < 0.001**
AWD at baseline	0.75 (0.54 to 0.95)	***p* < 0.001**	0.69 (0.51 to 0.87)	***p* < 0.001**
Subgroup 4				
BMT + SET[c]	–	–	–	–
BMT + NMES	−93 (−161.42 to −24.59)	***p* = 0.01**	−2.42 (−4.32 to −0.51)	***p* = 0.01**
Constant	191.14 (127.17 to 255.11)	***p* < 0.001**	8.25 (5.45 to 11.06)	***p* <0.001**
AWD at baseline	0.95 (0.76 to 1.13)	***p* < 0.001**	0.86 (0.68 to 1.03)	***p* < 0.001**
Subgroup 5				
BMT + NMES[c]	–	–	–	–
BMT + SET + NMES	160.72 (92.59 to 228.85)	***p* < 0.001**	4.25 (2.23 to 6.27)	***p* < 0.001**
Constant	46.46 (−21.16 to 114.07)	*p* = 0.18	3.35 (0.39 to 6.31)	***p* = 0.03**

continued

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TABLE 4 Output of right-censored Tobit regression models for AWD at 3 months to assess the effects of each subgroup for the complete cases in the ITT population (*continued*)

	Tobit regression (AWD raw data) Model 1[a]		Tobit regression (AWD square-root transformation) Model 2[b]	
Independent variables	**Coefficient (95% CI)**	***p*-value**	**Coefficient (95% CI)**	***p*-value**
AWD at baseline	1.02 (0.77 to 1.27)	***p* < 0.001**	0.9 (0.68 to 1.11)	***p* < 0.001**
Subgroup 6				
BMT[c]	–	–	–	–
BMT + SET + NMES	−144.24 (−231.51 to −56.97)	***p* < 0.001**	−4.1 (−6.56 to −1.64)	***p* < 0.001**
Constant	194.98 (113.51 to 276.44)	***p* < 0.001**	7.16 (3.79 to 10.53)	***p* < 0.001**
AWD at baseline	0.75 (0.48 to 1.03)	***p* < 0.001**	0.69 (0.47 to 0.91)	***p* < 0.001**
Subgroup 7				
BMT[c]	–	–	–	–
BMT + SET	80.06 (−4.59 to 164.71)	*p* = 0.06	2.34 (0.05 to 4.63)	***p* = 0.04**
Constant	111.4 (20.86 to 201.94)	***p* = 0.02**	5.94 (2.32 to 9.56)	***p* < 0.001**

a Model 1 Tobit regression model of AWD at 3 months = intercept + AWD (baseline) + subgroup + residual.
b Model 2 Tobit regression model of the square root of AWD at 3 months = intercept + square root of AWD (baseline) + subgroup + residual.
c Indicates being the reference category.

Notes
Subgroup 1 (Non-SET vs. SET): 148 uncensored observations, 12 right-censored observations.
Subgroup 2 (BMT + SET vs. BMT +SET + NMES): 79 uncensored observations, 11 right-censored observations.
Subgroup 3 (BMT vs. BMT + NMES): 69 uncensored observations, 1 right-censored observation.
Subgroup 4 (BMT + SET vs. BMT + NMES): 85 uncensored observations, 3 right-censored observations.
Subgroup 5 (BMT + NMES vs. BMT + SET + NMES): 72 uncensored observations, 8 right-censored observations.
Subgroup 6 (BMT + SET + NMES vs. BMT): 63 uncensored observations, 9 right-censored observations.
Subgroup 7 (BMT vs. BMT + SET): 76 uncensored observations, 4 right-censored observations.

Subgroup analysis

Subgroup analysis investigates the effect of the intervention among NMES + SET + BMT, NMES + BMT, SET + BMT and BMT. The subgroup analyses were defined as follows.

Subgroup analysis 1: Treatment effect in SET sites versus non-SET sites (NMES + SET + BMT and SET + BMT vs. NMES + BMT and BMT). The sample size in this group is *N* = 190 (*n* = 99 in SET and *n* = 91 in non-SET).

Subgroup analysis 2: Treatment effect of NMES in the SET sites (NMES + SET + BMT vs. SET + BMT). The sample size in this group is *N* = 99 (*n* = 47 in NMES + SET + BMT and *n* = 52 in SET + BMT).

Subgroup analysis 3: Treatment effect of NMES in the non-SET sites (NMES + BMT vs. BMT). The sample size in this group is *N* = 91 (*n* = 46 in BMT and *n* = 45 in BMT + NMES).

Subgroup analysis 4: Investigate if the treatment effect of (NMES + BMT) has a similar effect to (SET + BMT). The sample size in this group is *N* = 97 (*n* = 52 in BMT + SET and *n* = 45 in BMT + NMES).

Subgroup analysis 5: Determine if (NMES + SET + BMT) is more effective than (NMES + BMT). The sample size in this group is *N* = 92 (*n* = 45 in BMT + NMES and *n* = 47 in BMT + SET + NMES).

Subgroup analysis 6: Determine if (BMT) is more effective than (NMES + SET + BMT). The sample size in this group is *N* = 93 (*n* = 46 in BMT and *n* = 47 in BMT + SET + NMES).

Subgroup analysis 7: Determine if (BMT) is more effective than (BMT + SET). The sample size in this group is $N = 80$ ($n = 31$ in BMT and $n = 49$ in BMT + SET).

The sample sizes for the subgroups vary from 91 patients in Subgroup 3 (NMES + BMT vs. BMT) to 190 in Subgroup 1 (SET vs. non-SET).

The results of the Tobit regression models are found in *Table 20*, one for each subgroup. However, the interaction terms are not presented for Subgroups 2 through 7 due to problems of collinearity. We acknowledge the results of the subgroup analysis should be interpreted with caution due to the number of participants included in each subgroup analysis.

Table 20 indicates that SET had a significantly greater impact on both the square root of AWD compared to NMES (2.36 units; 95% CI 0.21 to 4.51; $p = 0.03$) as well as the AWD raw data compared to NMES (80.56 m; 95% CI 3.56 to 157.56; $p = 0.04$). However, when NMES was used as an adjunct to BMT and SET, there was a trend towards improved walking distances in the device arm, but this was not statistically significant, either for the square root of AWD (−0.19 units; 95% CI −2.45 to 2.06; $p = 0.87$) or for the AWD raw data (−18.01 m; 95% CI −98.81 to 62.78; $p = 0.66$). Additionally, there were no clear differences between BMT only and BMT with device use, either for the square root of AWD (−0.09 units; 95% CI −2.01 to 1.83; $p = 0.93$) or for the AWD raw data (−12.75 m; 95% CI −76.42 to 50.91; $p = 0.69$).

Post hoc analysis

Using only the compliance rules for SET and NMES, with all patients having BMT, we identified 124 (65.26%) compliers, but only 117 complete cases in the ITT population were used for the analysis. The results of post hoc analysis to compare the AWD between treatments in the compliers group are found in *Table 21*. The results indicate that there were no clear differences between the treatment arm and the control arm in AWD in the compliance post hoc analysis and the main analyses. Additional analyses for the primary outcome AWD in all the subgroups were performed (see *Report Supplementary Material 3*, *Tables 22–28*).

The outputs of the Wilcoxon rank-sum test for the raw data and the *t*-test for the transformed square-root AWD to compare treatment at baseline for the post hoc analysis can be found in *Report Supplementary Material 3*, *Table 29*. The distributions of AWD at baseline for treatment and control are presented in *Report Supplementary Material 3*, *Figure 5*.

The descriptive statistics of AWD at baseline are found in *Report Supplementary Material 3*, *Table 30*. Tables for the three strati, short, medium and long distances (set at <25%, 25–75% and >75%, respectively), for AWD can be found in *Report Supplementary Material 3*, *Table 31*.

For patients with a short baseline AWD, there was no significant difference between the two treatment arms, nor between type of centre (SET vs. non-SET) (see *Table 22*).

For patients with a medium baseline AWD, there was no clear difference between the two treatment arms, but there was a significant increase in the square root of the AWD at 3 months (3.081 units; 95% CI 1.01 to 5.14; $p = 0.004$) for a patient from a SET centre compared with a patient from a non-SET centre (see *Table 23*). Similarly, for AWD raw data for a patient from a SET centre compared to a non-SET centre, we also see an increase at 3 months (120.59 m; 95% CI 44.21 to 196.98; $p = 0.002$).

For patients with a long baseline AWD, there were significant differences between treatment arms and type of centre. From *Table 24*, we observe that there was a significant increase in the square root of the AWD at 3 months (2.877 units; 95% CI 0.51 to 5.25; $p = 0.019$) and in AWD raw data at 3 months

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TABLE 21 Output of the right-censored Tobit regression model for AWD at 3 months for patients who complied with treatment assigned for SET and NMES in the ITT population (*N* = 117)

	Tobit regression (AWD raw data)	Tobit regression (AWD square-root transformation)
	Model 1 **Coefficient (95% CI) *p*-value**	**Model 2** **Coefficient (95% CI) *p*-value**
AWD at baseline	0.8 (0.6 to 1) $p < 0.001$	0.73 (0.56 to 0.9) $p < 0.001$
Treatment[a]		
Control[b]		
Treatment[c]	20.77 (−43.34 to 84.88) $p = 0.52$	0.64 (−1.14 to 2.42) $p = 0.48$
Type of centre[d]		
Non-SET		
SET	139.37 (74.12 to 204.62) $p < 0.001$	3.97 (2.16 to 5.77) $p < 0.001$
Constant	88.52 (12.74 to 164.31) $p = 0.02$	5.19 (2.23 to 8.15) $p < 0.001$

a Control: local available exercise therapy (BMT and BMT + SET) as reference category.
b Control group includes BMT and BMT + SET.
c Treatment group includes BMT + NMES and BMT + SET + NMES.
d Non-SET exercise centres as reference category.

TABLE 22 Output of the right-censored Tobit regression model for AWD at 3 months for patients who walked a short distance at baseline in the ITT population (*N* = 40)

	Tobit regression (AWD raw data)	Tobit regression (AWD square-root transformation)
	Model 1 **Coefficient (95% CI) *p*-value**	**Model 2** **Coefficient (95% CI) *p*-value**
AWD at baseline	1.67 (−0.49 to 3.83) $p = 0.13$	1.18 (0.26 to 2.09) $p = 0.01$
Treatment[a]		
Control[b]		
Treatment[c]	9.01 (−113.72 to 131.75) $p = 0.88$	0.43 (−3.5 to 4.35) $p = 0.83$
Type of centre[d]		
Non-SET		
SET	73.43 (−47.66 to 194.51) $p = 0.23$	2.93 (−1.02 to 6.87) $p = 0.14$
Constant	54.58 (−145.69 to 254.86) $p = 0.58$	2 (−6.61 to 10.61) $p = 0.64$

a Control: local available exercise therapy (BMT and BMT + SET) as reference category.
b Control group includes BMT and BMT + SET.
c Treatment group includes BMT + NMES and BMT + SET + NMES.
d Non-SET exercise centres as reference category.

Notes
Model 1: Tobit regression model of the AWD at 3 months = intercept + AWD (baseline) + treatment + type of centre.
Model 2: Tobit regression model of the square root of AWD at 3 months = intercept + square root of AWD (baseline) + treatment + type of centre.

TABLE 23 Output of the right-censored Tobit regression model for AWD at 3 months for patients who walked a medium distance at baseline in the ITT population (*N* = 80)

	Tobit regression (AWD raw data)	Tobit regression (AWD square-root transformation)
	Model 1 Coefficient (95% CI) *p*-value	**Model 2 Coefficient (95% CI) *p*-value**
AWD at baseline	1.1 (0.5 to 1.69) $p < 0.001$	0.87 (0.42 to 1.32) $p < 0.001$
Treatment[a]		
Control[b]		
Treatment[c]	6.21 (−68.96 to 81.39) $p = 0.87$	0.22 (−1.81 to 2.24) $p = 0.83$
Type of centre[d]		
Non-SET		
SET	120.59 (44.21 to 196.98) $p = 0.002$	3.08 (1.03 to 5.14) $p = 0.004$
Constant	22.42 (−120.5 to 165.34) $p = 0.76$	2.99 (−3.72 to 9.7) $p = 0.38$

a Control: local available exercise therapy (BMT and BMT + SET) as reference category.
b Control group includes BMT and BMT + SET.
c Treatment group includes BMT + NMES and BMT + SET + NMES.
d Non-SET exercise centres as reference category.

Notes
Model 1: Tobit regression model of the AWD at 3 months = intercept + AWD (baseline) + treatment + type of centre.
Model 2: Tobit regression model of the square root of the AWD at 3 months = intercept + square root of AWD (baseline) + treatment + type of centre.

TABLE 24 Output of the right-censored Tobit regression model for AWD at 3 months for patients who walked a long distance at baseline in the ITT population (*N* = 40)

	Tobit regression (AWD raw data)	Tobit regression (AWD square-root transformation)
	Model 1 Coefficient (95% CI) *p*-value	**Model 2 Coefficient (95% CI) *p*-value**
AWD at baseline	0.81 (0.37 to 1.25) $p < 0.001$	0.82 (0.36 to 1.28) $p < 0.001$
Treatment[a]		
Control[b]		
Treatment[c]	120.55 (16.03 to 225.06) $p = 0.03$	2.88 (0.51 to 5.25) $p = 0.02$
Type of centre[d]		
Non-SET		
SET	189.96 (83.25 to 296.67) $p < 0.001$	4.03 (1.61 to 6.45) $p = 0.002$
Constant	−11.85 (−253.24 to 229.53) $p = 0.92$	1.48 (−8.81 to 11.77) $p = 0.77$

a Control: local available exercise therapy (BMT and BMT + SET) as reference category.
b Control group includes BMT and BMT + SET.
c Treatment group includes BMT + NMES and BMT + SET + NMES.
d Non-SET exercise centres as reference category.

Notes
Model 1: Tobit regression model of the AWD at 3 months = intercept + AWD (baseline) + treatment + type of centre.
Model 2: Tobit regression model of the square root of the AWD at 3 months = intercept + square root of AWD (baseline) + treatment + type of centre.

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TABLE 25 Serious adverse events in the ITT population by treatment arm

Variable	Treatment[a] *N* = 13	Control[b] *N* = 16	Total *N* = 29
Severity, *N* (%)			
Mild	1 (7.7%)	0 (0.0%)	1 (3.4%)
Moderate	2 (15.4%)	4 (25.0%)	6 (20.7%)
Severe	7 (53.8%)	6 (37.5%)	13 (44.8%)
Life-threatening or disabling	1 (7.7%)	5 (31.3%)	6 (20.7%)
Fatal	2 (15.4%)	1 (6.3%)	3 (10.3%)
Outcome, *N* (%)			
Recovered	10 (76.9%)	13 (81.3%)	23 (79.3%)
Recovering/improving	1 (7.7%)	0 (0.0%)	1 (3.4%)
Not recovered	0 (0.0%)	1 (6.3%)	1 (3.4%)
Fatal	2 (15.4%)	2 (12.5%)	4 (13.8%)
Not assessable	0 (0.0%)	0 (0.0%)	0 (0.0%)
Causal relationship to device, *N* (%)			
Definitely	0 (0.0%)	0 (0.0%)	0 (0.0%)
Probably	0 (0.0%)	0 (0.0%)	0 (0.0%)
Possibly	0 (0.0%)	0 (0.0%)	0 (0.0%)
Unlikely	2 (15.4%)	1 (6.3%)	3 (10.3%)
Not related	10 (76.9%)	15 (93.8%)	25 (86.2%)
Not assessable	0 (0.0%)	0 (0.0%)	0 (0.0%)
Not applicable	1 (7.7%)	0 (0.0%)	1 (3.4%)

a Treatment group includes BMT + NMES and BMT + SET + NMES.
b Control group includes BMT and BMT + SET.

(120.55 m; 95% CI 16.03 to 225.06; $p = 0.03$) for a patient in the device arm compared with a patient in the control arm. Similarly, there was a significant increase in the square root of the AWD at 3 months (4.033 units; 95% CI 1.61 to 6.45; $p = 0.002$) and in AWD raw data at 3 months (189.96 m; 95% CI 83.25 to 296.67; $p < 0.001$) for a patient from a SET centre compared with a patient from a non-SET centre.

Serious adverse events

Table 25 shows SAEs for the overall population categorised by treatment received. SAEs ($n = 29$) were reported in 24 patients, with all events being classified as either not related or unlikely to be related to the study device. The number of SAEs in the treatment arm was 13 and 16 in the control arm. Most of the events required hospitalisation, there were four deaths and the main primary System Organ Class term for the SAE's was gastrointestinal disorders.

Chapter 4 Health economic assessment

Introduction

This chapter conducts a within-trial analysis to calculate costs and QALYs over the 1-year time horizon of the NESIC trial. The analysis compares the use of the NMES plus local standard care versus local standard care alone in patients with IC in the UK NHS.

Analyses were undertaken in Stata® 16 (StataCorp LLC, College Station, TX, USA) and reported according to Consolidated Health Economic Evaluation Reporting Standards guidelines. The health economic analysis plan can be viewed here. Engagement of stakeholders and patients is described in another chapter.

No previous economic studies were found that compared treatment (NMES) versus control (no NMES). One previous economic study[30] compared SET to advice only and found that SET was more costly (€3407 vs. €2304) and more effective: 0.71 versus 0.67 QALYs, and a cost per QALY of €28,693 per QALY.

Methods

Resource use and costs

Costs were estimated from health-care resource use in the trial, recorded using patient diaries. The items included were the acquisition of the NMES device, admissions to hospital (including cause of admission), outpatient visits (including cause), visits to GP, practice nurse or other health-care professional, SET sessions and EA sessions. Patients also recorded whether the health care was provided by the NHS or privately funded. The primary analysis was from the perspective of the NHS and personal and social services, and secondary analyses included privately funded health care, health care not directly associated with IC or study treatments and productivity losses. The price year was 2019. No discount rate was applied as the time horizon is 1 year. Unit costs were taken from the literature, national NHS sources and manufacturers' list prices (see *Table 26*).

Health-related quality of life

QALYs were computed using the area-under-the-curve approach[35] from EQ-5D-5L collected in the trial at baseline, 3 and 12 months, assuming linear change in QoL between follow-ups. The primary analysis weighted the dimensions of the EQ-5D using the 'crosswalk' tariff (scoring algorithm)[36] recommended by NICE. A secondary analysis used an alternative UK tariff.[29]

Missing data

The pattern of missing data was examined. The primary analysis used multiple imputation with chained equations (MICE) to impute missing data items.[37] Imputations were carried out using predictive mean matching. It was found that matching using the nearest 5 neighbours (k = 5) and imputing 20 data sets (M = 20) gave stable results. Missing EQ-5D variables at baseline, 3, 6 and 12 months were imputed and QALYs were then estimated passively. Likewise, cost variable items were imputed separately and then total cost for each participant was estimated passively. The square root of average walking distance at each follow-up (rootAWD) was also used to improve the precision of the MICE predictions, with imputation of missing values. The treatment centre, treatment group, age, gender and rootAWD at baseline were used as independent predictive variables (with no imputation

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TABLE 26 Unit costs

	Costs	Source
NMES device	£249.99	Manufacturer
Hospital admissions for tests and procedures	£138	NHS reference costs; excess bed-days (2019)[16]
Daily wage	£97.36	Average hourly pay (ethnicity facts and figures)[31]
Angiogram	£111.00	NHS reference costs; diagnostic imaging (IMAG) (contrast fluoroscopy)[16] (2019)
Angioplasty (infrapopliteal)	£1418.00	NHS reference costs; Healthcare Resource Group (HRG) [percutaneous transluminal angioplasty (PTA) – single blood ves. 0-2][16] (2019)
Angioplasty (left leg)	£1418.00	NHS reference costs (HRG) (PTA – single blood ves. 0-2)[16] (2019)
Right illiac angioplasty	£1418.00	NHS reference costs (HRG) (PTA – single blood ves. 0-2)[16] (2019)
Bilateral endarterectomies	£5303.00	Patel *et al.*[32] (2019)
Endarterectomy	£5303.00	Patel *et al.*[32] (2019)
Right femoral endarterectomy	£5303.00	Patel *et al.*[32] (2019)
Right femoral popliteal bypass	£8857.00	NHS reference costs; bypass to tibial arteries[16] (2019)
Left bypass of popliteal artery	£8857.00	NHS reference costs; bypass to tibial arteries[16] (2019)
PTA of bypass graft	£8857.00	NHS reference costs; bypass to tibial arteries[16] (2019)
Hospital cost per day (if no procedure undertaken)	£459/day	NHS reference costs; excess bed-day cost[16] (2019)
Outpatient visit	£138.00	Vascular surgery follow-up
GP visit	£ 30/visit	NHS costs[33]
Practice nurse (9 minutes of practice nurse time)	£4.20/visit	Personal Social Services Research Unit 2019[34]
Physiotherapist (Band 7):	£57/visit	Personal Social Services Research Unit 2019[34]
SET group session, 60 minutes, 14 patients per group	£5.86/patient- session	60 minutes two physiotherapists (Band 5, £35/60 minutes, and Band 6, £47/60 minutes) for 14 patients
EA session	£3.50/session	7.5 minutes of practice nurse time Personal Social Services Research Unit 2019[34]

required). A secondary analysis undertook complete-case analysis (listwise deletion of subjects with any missing cost or EQ-5D items).

Cost-effectiveness analysis

The primary analysis was conducted on the ITT population. Mean costs and mean QALYs in each treatment group were estimated by using bivariate normal regression (seemingly unrelated regression). The probability that the net benefit of the treatment was greater than usual care was calculated assuming a bivariate normal distribution of costs and QALYs. Net benefit is defined as QALY associated with the therapy, valued at the decision-maker's willingness-to-pay threshold, less the costs of the therapy. The threshold was varied from zero to £50,000 per QALY, tracing out the cost-effectiveness acceptability curve.

The primary analysis included a binary indicator of randomised treatment group (NMES = 1, usual care = 0). Age (centred on mean), gender (male = 0) and rootAWD at baseline (centred on mean) were included

as independent control variables. In the analysis of QALY, the baseline EQ-5D was also included to correct for possible bias due to small imbalances in randomisation.[38]

A secondary (non-randomised) analysis compared the group of patients with SET versus those who did not have SET. A subgroup analysis was also undertaken to examine the impact on costs and QALYs of addition of NMES to patients with SET, and the addition of NMES to patients without SET. This was realised by including the NMES indicator variable, the SET indicator variable (SET = 1, no SET = 0), and an interaction term SET*NMES. The interaction term takes account of the possibility that the impact of the addition of NMES may be different for patients without SET compared with patients who also have SET.

Another sensitivity analysis modelled costs and QALYs separately using the generalised linear model with gamma family and log-link taking into account possible non-normal distribution of the dependent variable.

Secondary analyses

Table 27 provides a summary of the secondary analyses performed.

Decision modelling

As IC is a chronic disease, with long-term risks of serious complications including ulcers and amputation, the protocol for the study proposed the construction of a decision model to project the impact of the NMES intervention on costs and QALYs over a longer time horizon than 1 year. The literature review identified one study based on a model in a comparable patient population.[30] The model included health states of mild, moderate and severe claudication, CLI, major amputation and death (the model also included patients with asymptomatic PAD, which is not relevant in the context of the NESIC study). The probabilities of transitions between the states were obtained from individual patient data from two clinical studies.[30] The model extrapolated from the study data to obtain probabilities of secondary interventions (revascularisation) and progression of claudication over 5 years. However, there were insufficient numbers of patients with CLI in these studies to estimate rates of amputation after CLI and these probabilities were obtained from other literature.[39,40] The construction of such a model to extrapolate the treatment effect would only be appropriate if the RCT demonstrates an impact on QoL at 12 months that could reasonably be considered to be sustained over the longer term.

Budget impact

The protocol for the study proposed a budget impact assessment, should the treatment be demonstrated to be cost-effective.

TABLE 27 Summary of secondary analyses

Primary analysis	Secondary analysis
NHS health care, related with IC or study treatments	Including any health care, whether privately or publicly funded
Crosswalk EQ-5D scoring algorithm	Alternative EQ-5D scoring algorithm
Multiple imputation of missing values	Complete case analysis
NMES vs. usual care in the ITT population	SET vs. no SET
NMES vs. usual care in the ITT population	Analysis of impact of NMES vs. usual care separately in the subgroup of patients with SET and the subgroup of patients without SET

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Results

Cost-effectiveness

Tables 28 and *29* show the mean NHS resource use and costs used by the patients in the study over 3 months and 1 year, for patients with complete follow-up data over those time periods. *Figure 4* shows these data graphically. At 1 year, the mean difference in costs between the treatment and control groups was £130, with the initial cost of the device being partially offset by fewer inpatient admissions.

Primary cost-effectiveness analysis: treatment versus control

Table 30 shows the unadjusted mean cost and QALY in the treatment and control groups, and *Table 31* shows the coefficients of the bivariate regression, adjusted for age, gender and rootMWD in the primary cost-effectiveness analysis. This includes multiple imputations of missing values. *Table 32* show the extent of missing data at each time point. The estimated incremental cost per QALY is 188/0.0034 = £55,294/QALY. With a cost-effectiveness threshold of £20,000, the probability that the intervention is cost-effective is 35%, or 42% at a threshold of £30,000 (see *Figure 5*). None of these effects is significant at the 5% significance level. A parametric cost-effectiveness plane can be seen in *Figure 6*.

TABLE 28 Resource use and costs – treatment vs. control: at 3 months, complete cases

Item	Treatment[a] (*N* = 75)			Control[b] (*N* = 71)			Difference (treatment – control)
	Mean units	Unit cost	Total	Mean units	Unit cost	Total	
Associated with the intervention							
Device	1.00	249.99	249.99	0.00	0.00	0.00	249.99
SET	6.87	5.86	40.26	7.53	5.86	44.13	−3.87
EA	1.00	3.50	3.50	1.00	3.50	3.50	0.00
Costs incurred by patients							
Inpatient	0.23	6.43	1.48	0.00	0.00	0.00	1.48
Outpatient	0.67	138.00	92.46	0.69	138.00	95.22	−2.76
GP visit	0.55	30.00	16.50	0.48	30.00	14.40	2.10
Nurse visit	0.43	4.20	1.81	0.35	4.20	1.47	0.34
Health-care professional visit	0.19	57.00	10.83	0.11	57.00	6.27	4.56
Total w/o social costs	**416.04**			**165.16**			**250.88**
Social costs per patient							
Productivity losses (days per patient)	0	97.36	0	0.0714	97.36	6.95	−6.95
Out-of-pocket expenses (£ per patient)	–	–	1.60	–	–	0.1019	1.4981
Total	**417.64**			**172.21**			**245.43**

a Treatment group includes BMT + NMES and BMT + SET + NMES.
b Control group includes BMT and BMT + SET.

Notes
Units expressed in mean minutes per patient (except device, one unit per patient; productivity losses, days; out of pocket expenses, pounds). Complete cases are those observations with QoL and cost data for baseline and at 3 months.

TABLE 29 Resource use and costs – treatment vs. control: at 12 months, complete cases

	Treatment[a] (*N* = 75)			Control[b] (*N* = 71)			
Item	**Mean visits**	**Unit cost**	**Total**	**Mean visits**	**Unit cost**	**Total**	**Difference (t-c)**
Device	1.00	249.99	249.99	0.00	0.00	0.00	249.99
Inpatient admission	0.84	130.95	110.00	1.94	113.09	219.40	−109.40
Outpatient visit	2.15	138.00	296.24	2.15	138.00	297.38	−1.14
GP visit	1.84	30.00	55.20	1.79	30.00	53.66	1.54
Nurse visit	1.05	4.22	4.42	0.92	4.22	3.85	0.57
Health-care professional	0.56	57.00	31.92	0.69	57.00	39.34	−7.42
SET	6.87	5.86	40.24	7.54	5.86	44.16	−3.92
EA	1.00	3.50	3.50	1.00	3.50	3.50	0.00
Total	**791.51**			**661.29**			**130.22**
Social costs per patient							
Productivity losses (days per patient)	1.2282	97.36	119,57	0.7984	97.36	77.73	41,84
Out of pocket expenses (£ per pat.)	–	–	0.44	–	–	2.13	−1.69
Total	**911,52**			**740,86**			**170,66**

a Treatment group includes BMT + NMES and BMT + SET + NMES.
b Control group includes BMT and BMT + SET.

Note
Complete cases are those observations with QoL and cost data for baseline, 3, 6 and 12 months. A total of 146 observations meet this requirement (treatment, 75; control, 71).

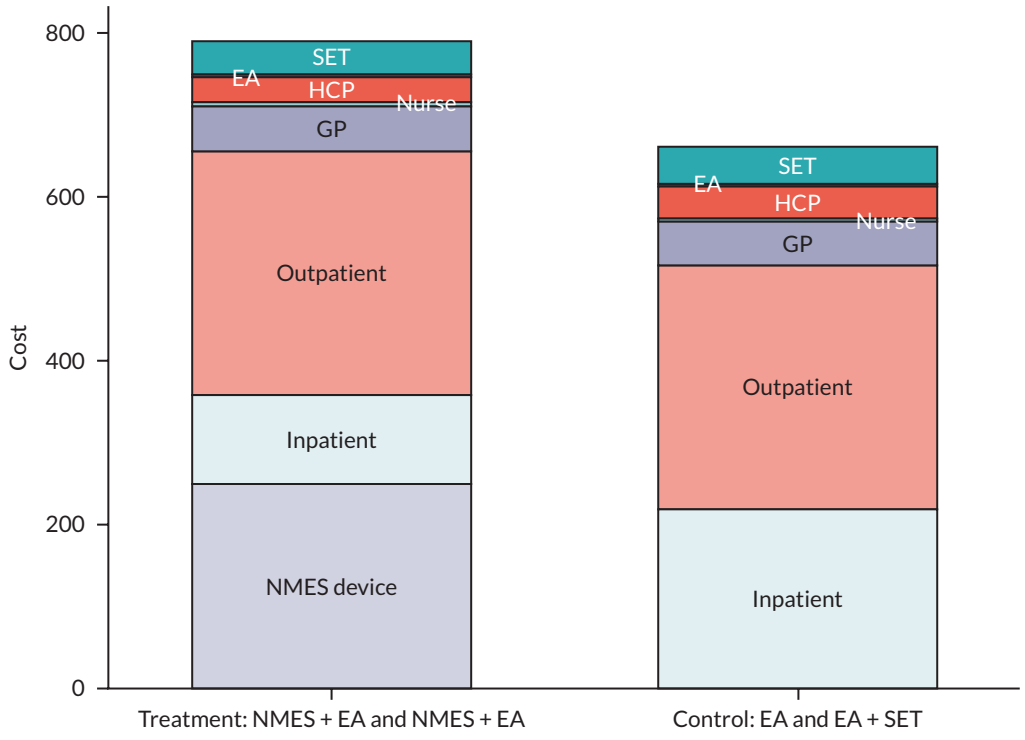


FIGURE 4 Cost comparison, treatment vs. control at 12 months, complete cases.

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TABLE 30 Treatment vs. control (*N* = 190): at 12 months

	Treatment[a]			Control[b]					
	Mean	SE	95% CI	Mean	SE	95% CI	Difference	SE	95% CI
Cost	777.86	110.40	(556.57 to 999.15)	614.59	159.27	(298.32 to 930.87)	163.26	195.59	(−222.98 to 549.52)
QALY	0.6459	0.0214	(0.6032 to 0.6886)	0.6355	0.0182	(0.5992 to 0.6718)	0.0104	0.0270	(−0.043 to 0.0637)

SE, standard error.
a Treatment group includes BMT + NMES and BMT + SET + NMES.
b Control group includes BMT and BMT + SET.

Note
Includes multiple imputations of missing values.

TABLE 31 Treatment vs. control: seemingly unrelated regressions (*N* = 190)

	Coefficient	SE	*p*-value
Total costs			
Treatment[a]	187.77	196.03	0.338
Age (age − mean)	6.69	11.21	0.551
Gender (female)	357.19	229.56	0.120
Root AWD baseline	−0.0005	0.0008	0.523
Constant	553.06	154.81	<0.000
1-year QALY			
Treatment[a]	0.0034	0.0191	0.859
Age	0.0010	0.0011	0.369
Female	0.0134	0.0112	0.546
Baseline QoL (EQ-5D)	0.6246	0.0522	<0.000
Root AWD baseline	1.24e-07	8.55e-08	0.147
Constant	0.2346	0.0346	<0.000

SE, standard error.
a Treatment group includes BMT + NMES and BMT + SET + NMES.

Note
Includes multiple imputations of missing values.

Secondary analyses

SET versus no SET

As a secondary analysis, the costs and QALY associated with SET versus no SET were compared (see *Table 33*). The incremental cost per QALY of SET versus no SET was 301/0.0232 = £12,974 per QALY. With a cost-effectiveness threshold of £20,000, the probability that the intervention is cost-effective is 58%, or 69% at a threshold of £30,000 (see *Figure 7*).

Addition of neuromuscular electrical stimulation to supervised exercise therapy versus addition of neuromuscular electrical stimulation to patients without supervised exercise therapy

The impact of adding NMES for patients with and without SET was estimated by adding an interaction term to the regression model (see *Table 34*). *Table 35* calculates the margins associated with this

TABLE 32 Missing data at each time point

		Treatment[a]		Control[b]	
		Resource use	EQ-5D	Resource use	EQ-5D
Baseline					
	Complete	91	91	97	97
	Missing	1	1	1	1
3 Months					
	Complete	85	86	84	84
	Missing	7	6	14	14
6 Months					
	Complete	79	80	78	80
	Missing	13	12	20	18
12 Months					
	Complete	77	76	76	76
	Missing	15	16	22	22

a Treatment group includes BMT + NMES and BMT + SET + NMES.
b Control group includes BMT and BMT + SET.

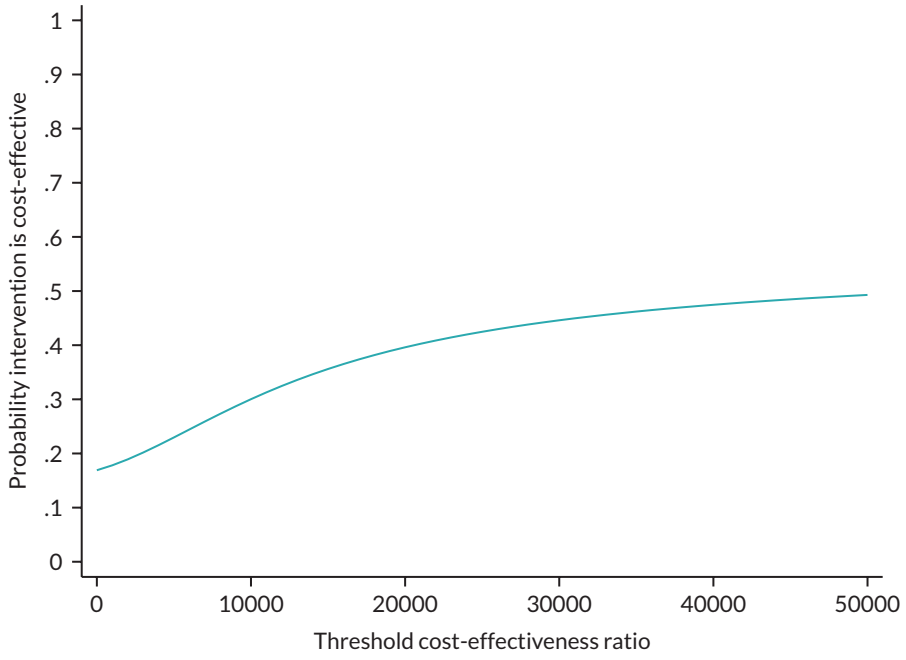


FIGURE 5 Treatment vs. control: cost-effectiveness acceptability curve.

regression model, that is, the mean costs and QALYs for four groups of patients: with and without SET, and with and without NMES.

For patients without SET, adding NMES increased costs by £338 and QALYs by 0.0131, and was associated with an incremental cost per QALY of £25,801/QALY. For patients with SET, adding NMES would not increase QALY. However, none of these effects is significant at the 5% significance level.

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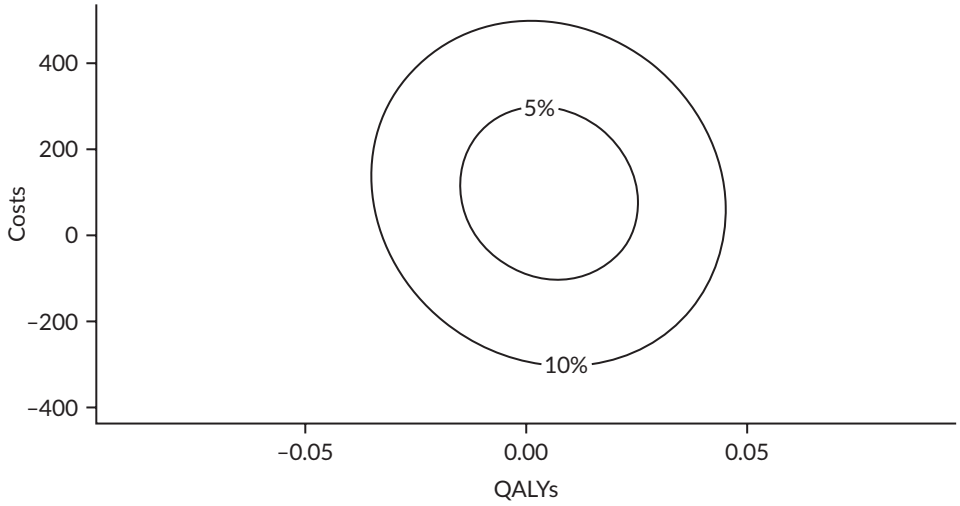


FIGURE 6 Cost-effectiveness plane. Confidence ellipses calculated using means and covariances from the seemingly unrelated regression (R package contour and mvtnorm).

TABLE 33 Supervised exercise therapy vs. non-SET: seemingly unrelated regression (*N* = 190)

	Coefficient	SE	*p*-value
Total costs			
SET (vs. non-SET)	300.96	193.13	0.119
Age (age − mean)	7.84	11.17	0.483
Gender (female)	282.27	227.80	0.216
Root AWD baseline	−0.0004	0.0008	0.623
Constant	496.11	156.43	0.002
1-year QALY			
Treatment[a]	0.0232	0.0197	0.239
Age	0.0011	0.0011	0.345
Female	0.0081	0.0222	0.345
Baseline QoL (EQ-5D)	0.6290	0.0519	<0.000
Root AWD baseline	1.27e-07	8.47e-08	0.134
Constant	0.2226	0.0352	<0.000

a Treatment group includes BMT + NMES and BMT + SET + NMES.

Note
Includes multiple imputation of missing values.

Complete case

Table 36 shows the results for patients who had no missing cost or EQ-5D observations (complete case). NMES does not result in a QALY gain.

Alternative EQ-5D scoring algorithm

Table 37 shows the results using an alternative scoring algorithm for the EQ-5D. The incremental cost per QALY would be 135/0.0118 or £11,440 per QALY.

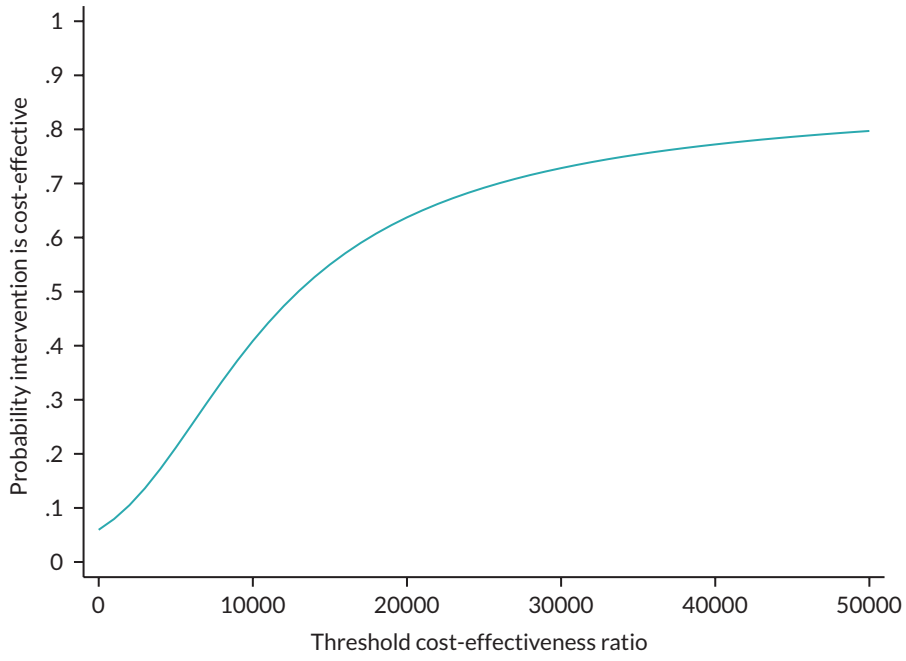


FIGURE 7 Supervised exercise therapy vs. non-SET: cost-effectiveness acceptability curve.

TABLE 34 Subgroup analysis: treatment vs. control in patients with SET and without SET. Seemingly unrelated regression with interaction terms (*N* = 190)

	Coefficient	SE	*p*-value
Total costs			
Treatment[a]	338.39	268.07	0.207
Group (SET)	442.63	261.22	0.090
NMES*SET	−287.41	381.15	0.451
Age (age − mean)	7.23	11.13	0.516
Gender (female)	284.16	229.48	0.216
Root AWD baseline	−0.0005	0.0008	0.557
Constant	335.84	201.78	0.096
1-year QALY			
Treatment[a]	0.0133	0.0280	0.634
SET	0.0325	0.0282	0.250
NMES # SET	−0.0189	0.0399	0.636
Age	0.0010	0.0011	0.354
Female	0.0076	0.0223	0.733
Root AWD baseline	1.26e-07	8.52e-08	0.140
Baseline QoL (EQ-5D)	0.6294	0.0518	<0.000
Constant	0.2159	0.0389	<0.000

a Treatment group includes BMT + NMES and BMT + SET + NMES.

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TABLE 35 Interpretation of the subgroup analysis (*N* = 190)

	Treatment[a]	Control[b]	Differences
Mean costs			
No SET	674.24	335.84	338.4
SET	829.46	778.48	50.98
Differences	155.22	442.64	287.42, $p = 0.451$
Mean QALY			
No SET	0.229	0.2159	0.0131
SET	0.243	0.2484	−0.0054
Differences	0.014	0.0325	0.0185, $p = 0.636$
ICERs by subgroups			
No SET	Treatment vs. control: 25,801 £/QALY		
With SET	Treatment is dominated by control		
ICERs comparing SET vs. no SET			
SET vs. no SET (non-randomised comparison)	Treatment[a]: 11,087 £/QALY	Control[b]: 13,600 £/QALY	

a Treatment group includes BMT + NMES and BMT + SET + NMES.
b Control group includes BMT and BMT + SET.

TABLE 36 Treatment vs. control: seemingly unrelated regression. Complete case (*N* = 146)

	Coefficient	SE	*p*-value
Total costs			
Treatment[a]	168.88	231.41	0.466
Age (age − mean)	9.83	12.66	0.437
Gender (female)	386.70	261.50	0.139
Root AWD baseline	−0.0005	0.0009	0.557
Constant	−82.89	891.76	0.926
1-year QALY			
Treatment	−0.0057	0.0203	0.776
Age	0.0016	0.0011	0.164
Female	0.0197	0.0230	0.391
Baseline QoL (EQ-5D)	0.6531	0.0516	<0.000
Root AWD baseline	1.60e-07	8.72e-08	0.066
Constant	0.1120	0.0802	0.163

SE, standard error.
a Treatment group includes BMT + NMES and BMT + SET + NMES.

Note
No missing-data imputation has been carried out.

TABLE 37 Treatment vs. control: seemingly unrelated regression. Alternative EQ-5D scoring algorithm

	Coefficient	SE	*p*-value
Total costs			
Treatment[a]	134.65	207.16	0.516
Age (age – mean)	7.03	11.04	0.524
Gender (female)	312.55	229.94	0.174
Root AWD baseline	−0.0005	0.0008	0.547
Constant	607.16	181.87	0.001
1-year QALY			
Treatment[a]	0.0118	0.0188	0.529
Age	0.0014	0.0010	0.173
Female	0.0291	0.0219	0.186
Baseline QoL (EQ-5D)	0.6908	0.0501	>0.000
Root AWD baseline	9.23e-08	8.39e-08	0.321
Constant	0.2636	0.0358	>0.000

SE, standard error.
a Treatment group includes BMT + NMES and BMT + SET + NMES.

Note
Using Delvin tariff instead of crosswalk. Multiple imputations.

Including costs unrelated to intermittent claudication and patient out-of-pocket expenses

Table 38 shows the results if costs of health care that was unrelated to IC are included, along with patient out-of-pocket expenses. The incremental cost per QALY would be 460/0.009 or £51,111 per QALY.

Alternative models for the distribution of costs and quality-adjusted life-years

Table 39 shows the results if the dependent variables (costs and QALY) are modelled using a generalised linear model with a gamma family and log-link. The effect of treatment is not statistically significant at the 5% level.

Discussion

This chapter has conducted a within-trial economic evaluation of treatment (NMES) versus control (no NMES) for patients with IC. The estimated incremental cost per QALY is £55,294/QALY. With a cost-effectiveness threshold of £20,000, the probability that the intervention is cost-effective is 35%. None of these effects is significant at the 5% significance level. Hence NMES is not considered cost-effective at conventional thresholds in the UK.

The analysis has considered several sensitivity and subgroup analyses. A subgroup analysis in centres that offer SET as local standard care found that the cost per QALY was about £25,000/QALY. An analysis that used an alternative scoring system for the EQ-5D found the cost per QALY was about £11,000/QALY. No other secondary analyses changed the main conclusion that NMES is not cost-effective.

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TABLE 38 Treatment vs. control, including costs unrelated to IC: seemingly unrelated regressions (*N* = 190)

	Coefficient	SE	*p*-value
Total costs			
Treatment[a]	460.23	525.07	0.381
Age (age – mean)	−14.24	28.36	28.35
Gender (female)	−204.57	574.91	0.722
Root AWD baseline	−0.0037	0.0022	0.091
Constant	1597.23	477.14	0.001
1-year QALY			
Treatment[a]	0.0090	0.0199	0.650
Age	0.0008	0.0011	0.454
Female	0.0132	0.0219	0.547
Baseline QoL (EQ-5D)	0.6308	0.0514	>0.000
Root AWD baseline	9.37e-08	8.59e-08	0.275
Constant	0.2340	0.0369	>0.000

SE, standard error.
a Treatment group includes BMT + NMES and BMT + SET + NMES.

Note
Non-related costs included. Multiple imputation data.

TABLE 39 Generalised linear models with gamma family and log-link (separately for cost and QALY)

	Coefficient	SE	*p*-value
Total costs			
Treatment[a]	0.3479	0.2709	0.199
Age (age – mean)	0.0081	0.0153	0.599
Gender (female)	0.5139	0.3076	0.095
Root AWD baseline	−8.81e-07	1.12e-06	0.432
Constant	6.2833	0.2544	<0.000
1-year QALY			
Treatment[a]	−0.0090	0.0431	0.833
Age	0.0018	0.0023	0.452
Female	0.0205	0.0473	0.665
Baseline QoL (EQ-5D)	1.2900	0.1883	<0.000
Root AWD baseline	2.04e-07	1.90e-07	0.283
Constant	−1.2984	0.1325	0.000

SE, standard error.
a Treatment group includes BMT + NMES and BMT + SET + NMES.

Chapter 5 Discussion

Interpretation of results

NESIC is the first multicentre, pragmatic randomised study to investigate the adjuvant benefit of NMES in patients with IC receiving localised standard care. The results show a treatment hierarchy for patient benefit. Patients in the NMES group in combination with SET and BMT had the most improved AWD at 3 months, followed by patients with access to SET and BMT, and lastly those patients who received BMT alone.

The results of this study add to a growing body of evidence that supports the benefit of SET in improving walking distances in patients with IC.[6–8,41] For this reason, NICE recommends 2 hours of supervised exercise per week for 3 months as first-line management of PAD. Despite this evidence and the current recommendations, it has been shown that SET remains an underutilised tool. Therefore, novel approaches that can be used as an adjunct to local available therapy, designed to increase physical activity in patients with PAD, such as NMES, may have an implication in the first-line treatment of IC.

While this study shows that there is no clear difference in AWD at 3 months between those patients who received NMES compared to standard care alone, there was a non-significant trend suggesting an advantage to NMES when used in combination with SET and BMT. This, taken with the previous body of evidence of improved walking distance, suggests this may be an area for further review.

The primary outcome finding contradicts the outcome in the RCT by Babber *et al*.,[21] which found a significant improvement in MWD after using NMES for 30 minutes daily for a 6-week duration when used independently and also as an adjunct to SET. Considering reasons for this discrepancy, it is noted that the previous study did not reach the recruitment target, while in this study we have also hypothesised that there may be reduced compliance with EA when supplied with an NMES device.

Interestingly, the post hoc analysis showed that patients with a longer baseline MWD have a significantly improved AWD with NMES and SET compared to those with shorter baseline MWD. Neither SET nor NMES was significant in improving AWD in patients who walked <100 m at baseline (N = 40). In contrast, both SET and NMES significantly improved AWD at 3 months for patients who could walk further than 340 m at baseline (N = 40). Perhaps, non-invasive therapies are less effective on those with a poor baseline walking distance and this cohort of patients require surgical intervention. It is noted that these numbers are small but warrant an area for further research.

Health-related quality of life

For health-related QoL, the SF-36 showed no evidence of a difference between the two groups over the follow-up time points for the overall population. The EQ-5D-5L scores significantly improved in the NMES group at 3 months compared to the control group but this was not sustained. After the final 12-month follow-up, there was a significant difference in the disease-specific QoL ICQ improvement between the groups, benefitting the control group. This contrasts with the studies conducted by Babber *et al*.,[21] in which both generic and disease-specific QoL scores showed a significant improvement in the proof-of-concept study, and ICQ scores improved significantly in the NMES group of the RCT. This may be due to the differences in the length of follow-up.

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Haemodynamic assessments

Haemodynamic assessments were performed to better understand the underlying mechanisms associated with any changes attributable to the NMES device. There were no clear changes in VF, TAMV or blood flux when the device was turned on, suggesting no improvement in arterial flow to the leg. This contradicts the RCT by Babber *et al.*,[21] which found significant increases in VF and TAMV when the device was switched on at baseline and at week 6, although this was not maintained after device cessation.

Compliance

Compliance with intervention is a vital aspect of the successful management of PAD; 69.7% of those patients with access to SET attended a minimum of 50% of the classes. Current data on compliance with SET in patients with PAD are problematic as the definition of compliance differs between studies and the duration of SET programmes varies widely between research trials. A 2016 systematic review by Harwood *et al.*[42] of 67 trials showed an average of 75.1% of patients reportedly completed a SET programme; however, only one paper defined a minimal attendance required for SET programme completion.

Compliance to the device in this study was 73.9%, which was less than what was observed in the 6-week pilot study (97%) and subsequent RCT (96%).[21] During the course of this study, no participants contacted the investigators for additional support and most reported good tolerability to device use; 87.5% of device users stated the device was 'very easy' to use and 63.6% of device questionnaire respondents stated that they could have used the device more frequently.

The NESIC study also collected data on compliance to EA (52.1%) but this had the highest percentage of missing data (20.5%).

A sensitivity analysis, using only the compliance rules for SET and NMES, with all patients having EA, showed no clear differences from the main analysis (including subgroup analyses).

Cost-effectiveness analysis

There was no significant difference in costs or QALYs between NMES and usual care, in any of the cost-effectiveness analyses undertaken. The subgroup analyses show that QALYs are slightly greater in the SET group compared with no SET, but this does not reach statistical significance. The main cost-effectiveness analysis estimated an ICER that was £55,294 per QALY. However, the gain in QALY was very small and statistically insignificant.

There were some secondary and subgroup analyses where, based on mean costs and QALYs, NMES showed ICERs lower than £30,000 per QALY. Adding NMES to patient care if SET is unavailable gave an ICER of £25,801 per QALY. However, this analysis is ad hoc (not included in the study protocol) and non-randomised. The use of the Devlin scoring algorithm for the EQ-5D gave an ICER of £11,440 per QALY. This algorithm has so far not been recommended by NICE. Other secondary analyses did not show cost-effectiveness at usual NICE thresholds.

Given that the RCT has shown no measurable or clinically relevant difference between NMES and usual care at 1 year, there would be little policy relevance in extrapolating this difference over the longer term in a structured decision model. Likewise, there is little policy relevance in estimating the budget impact of a treatment that does demonstrate cost-effectiveness and is unlikely to be implemented in the population represented by the RCT.

Patient and public involvement

Introduction

Patient and public involvement (PPI) improves the quality of research studies and their relevance for patients and the health service. This includes improving the way the research is prioritised, designed, undertaken, communicated and disseminated.[43] Commitment and interest in involvement has expanded in recent years, with many researchers developing processes to involve patients and the public in clinical research.[44] The NIHR have supported this by developing infrastructure through the INVOLVE network.

The NESIC collaborators developed a PPI partnership conducted in line with INVOLVE recommendations,[45] engaging the public as early as possible and throughout the cycle of the research project to maximise the benefit of the public/patient perspective. Sydney Chapple was approached to join the trial and agreed to act as a lay patient representative.

Aim of patient and public involvement in NESIC

The aim of the lay member role in NESIC was to support the following areas of work:

- Assist with the design stage of the trial to ensure that the research questions and outcomes were relevant to those with the lived experience of the condition.
- Join the TSC and attend meetings.
- Input and suggestions to aid recruitment and retention.
- Create and review patient facing content.
- Aid with dissemination of trial results to ensure results reach the people whom the research was intended for.

Role description

In line with INVOLVE guidance, a role description was provided to the lay patient to detail the expectations, commitment levels of the post, details of reimbursement for travel/time and resources to access for further PPI support (see *Report Supplementary Material 2*).

Set-up

During the set-up phase of the trial, the lay representative reviewed all participant-facing documents including, but not limited to, the participant information sheets, informed consent forms and recruitment advertisements. Amendments were made in line with his suggestions.

During the study

The PPI patient attended the first TSC meeting and contributed and co-approved the TSC charter. During the study, he attended TSC meetings, usually via teleconference due to availability and the COVID-19 pandemic. He offered active input into discussions, reviewed amendments and provided sound advice.

The trial manager made contact with the PPI representative following involvement activities thanking him for his involvement and providing him with feedback as to the outcome of his involvement – for example, the changes to the participant information sheet (such as summarising the follow-up period in a table) that were made as a result of his suggestions.

The trial manager had telephone calls with the PPI patient between meetings to ensure he was kept up to date with trial progress so that he felt connected to the research and motivated to continue the involvement. He was also sent monthly study newsletters.

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Study results

The PPI representative will be invited to attend the TSC/DMC results meeting to help provide a public/patient perspective on the interpretation of trial findings.

Dissemination

The PPI representative was involved in reviewing sections of this final report including the Plain English summary. He will also be asked to review the results newsletter for dissemination to study participants. The PPI representative contributed to the design of the dissemination plan to ensure the study results reach the people whom the research was intended for – both participants and the wider patient/public community – and in a format that is understandable to them.

Evaluating impact

With their lived experience of a condition as well as their experience of involvement in the research project, public partners provide valuable insight into the evaluation of the impact of the research project as well as the impact that the public involvement has on the project.

It is difficult to quantify what extent PPI influenced any particular outcome. It is clear that discussions during committee meetings and telephone calls with the trial manager helped the research team improve enrolment and retention of participants.

Summary

Evaluating the impact of the public involvement in a project is important to inform future involvement activities. Based on the findings of the PPI representative involvement feedback, when designing future studies the research team would aim to:

- include more than one lay patient representative to accurately reflect the patient population
- ensure that the trial manager communicates with the lay members before and after study meetings to explain any study reports and debrief
- ensure public partners are paid for their time in line with the policy on payment of fees and expenses for members of the public actively involved with The Centre for Engagement and Dissemination www.nihr.ac.uk/documents/payment-guidance-for-researchers-and-professionals/27392
- gain support from patient groups – that is, the Circulation Foundation.

Equality, diversity and inclusion

Geographically diverse recruitment sites were selected to act as participating centres.

These included sites located in local authorities with the highest UK deprivation indices and centres with low research activity where patients may not have had access to research participation.

During the NESIC study, we were contacted by patients who found our study online and wished to participate, which improved accessibility for all patients.

Data relating to equality and diversity (age, gender, ethnicity, recruitment site) were collected from study participants at the initial visit. Data were monitored on a monthly basis by the TMG to ensure that the research sample was representative of the IC population. Any factors limiting equality and diversity in recruitment were reviewed and addressed.

Furthermore, the research team was diverse, interdisciplinary, included patient representatives and had substantial expertise in the delivery of large RCTs in vascular disease.

Generalisability

The trial was designed to be as pragmatic as possible in order to maximise the generalisability of any findings. Patients were recruited from 11 large NHS trusts distributed between those that provide SET and those that provide best medical practice only.

Strengths of NESIC

1. This is the first large RCT looking at the adjuvant benefit of NMES in patients with IC.
2. Generalisability of the results across vascular units that provide a supervised exercise programme and those that provide BMT only.
3. Compliance data collected separately for NMES, SET and EA, with clear definitions on what is deemed as compliant.

Limitations of NESIC

1. Absolute walking distance was used as the primary outcome measure. There was a large variability in the baseline AWD in both groups, with right-skewed distribution. We did not stratify by baseline AWD but the analysis was adjusted by baseline AWD.
2. Only 160 patients had analysable primary outcome data due to missing treadmill data at baseline and/or 3 months.
3. Absence of a sham device comparator. This was considered during the design stage but it was deemed very difficult to blind the research team or participant to the study allocation due to the patient setting the stimulation level to a threshold where calf contractions are visible. This may impact the study findings by introducing bias and we hypothesise that there may be reduced compliance with EA when supplied with an NMES device.

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Chapter 6 Conclusions

Overall conclusions

This multicentre randomised trial demonstrates the clear benefit of SET for PAD. The addition of NMES may have an adjuvant benefit on AWD, particularly in patients with mild IC. From the subgroup analysis we can conclude that SET and NMES are most effective in patients who are able to walk longer distances at baseline.

For secondary outcomes, the NMES device did not show any improvements in haemodynamic measurements when switched on, nor any significant improvements in generic or disease-specific QoL at the end of the follow-up period. Establishing exercise compliance remains challenging in the PAD cohort, in particular for exercise in a patient's own time.

Implications for health care

Findings from this trial suggest that all IC patients should have access to a SET programme and changes to such programmes may need to be made to encourage and/or retain participants. NMES may be an effective adjunct to SET and in patients with a good baseline walking distance.

Recommendations for research

- Randomised controlled trial of NMES as an adjunct to SET in IC patients stratified by baseline AWD.
- Research to examine the poor patient motivation and adherence to SET.
- Research to evaluate the long-term effectiveness of SET programmes on MWD and secondary outcomes such as QoL and long-term engagement in physical activity.

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Trial applicants

Alun Davies, Joseph Shalhoub, Adarsh Babber, Manjit Gohel, Robert Hinchliffe, James Coulston, Bruce Braithwaite, Ian Chetter, David M Epstein, Gerard Stansby and Francesca Fiorentino.

Trial Management Group

The Trial Management Group comprised Professor Alun Davies (as chief investigator), Ms Laura Burgess (as trial manager), Ms Sasha Smith [as trial manager (maternity cover)], Ms Consuelo Nohpal de la Rosa (as statistician), Dr Francesca Fiorentino (as senior statistician) and Ms Natalia Klimowska-Nassar (as Operations Manager).

Imperial Clinical Trials Unit

The following members were part of the wider ICTU trial team: Amanda Bravery, Kayode Disu, Nayan Das, Ayse Depsen, Smita Das (InForm database team); Ginny Picot, Eloise Britten and Jonathan Dao (quality assurance).

Department of Surgery and Cancer, Imperial College

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Trial Steering Committee

We would like to thank Professor Andrew Bradbury (Chair, Sampson Gamgee Professor of Vascular Surgery), Professor Jonathan Beard (Consultant Vascular Surgeon), Dr Louise Brown (Medical Statistician) and Mr Sydney Chapple (lay member), who provided invaluable input and advice as the independent lay member over the course of the study.

Data Monitoring Committee

The team would also like to thank the Independent Data Monitoring Committee members: Professor Julie Brittenden (Chair, Professor of Vascular Surgery), Mr Chung Sim Lim (Consultant Vascular Surgeon) and Dr Stephen Gerry (Medical Statistician) for their support and guidance.

Patient and public involvement

Sydney Chapple was involved in the original design during the grant-application stages and was an active member of the Trial Steering Committee throughout the study. Sydney's involvement is detailed in the PPI lay-person description (see *Report Supplementary Material 2*).

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Data cleaning

Data cleaning was performed by the trial manager and study statistician.

Local research teams

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Laura Burgess (https://orcid.org/0000-0001-7491-7557) (Trial Manager) managed and monitored the trial as trial manager, assisted with acquisition of the data and drafted relevant chapters and approved the final version of the report.

Sasha Smith (https://orcid.org/0000-0001-9843-5368) [Trial Manager (maternity cover)] managed and monitored the trial as trial manager, assisted with acquisition of the data and approved the final version of the report.

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Natalia Klimowska-Nassar (https://orcid.org/0000-0003-3655-7436) (Operations Manager) was responsible for the design, conduct and dissemination and final approval.

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of analysis and dissemination, drafting relevant chapters and coordination of the report including final approval.

Laura Burgess, **Alun H Davies**, **Francesca Fiorentino**, **Consuelo Nohpal de la Rosa** and **David M Epstein** were responsible for drafting this report, although all authors provided comments on drafts and approved the final version.

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Ethics and research and development approvals

A favourable ethical opinion was given by the National Research Ethics Service Committee London-Surrey on 20 November 2017 (reference number 17/LO/1918).
Study-wide governance review was undertaken by the North-West London Clinical Research Network (CRN) in November 2017. Research and development (R&D) NHS approvals were granted at the original eight participating sites January–June 2018. The study was granted Health Research Authority approval, January 2018. R&D NHS approvals were granted at the additional three participating sites November–December 2018.

Data-sharing statement

All data requests should be submitted to the corresponding author for consideration. Access to anonymised data may be granted following review. Data-access requests are handled on a case-by-case basis and will be reviewed by the corresponding author, Trial Management Group and sponsor. A record of all access to data will be maintained by the Imperial College Archive team.

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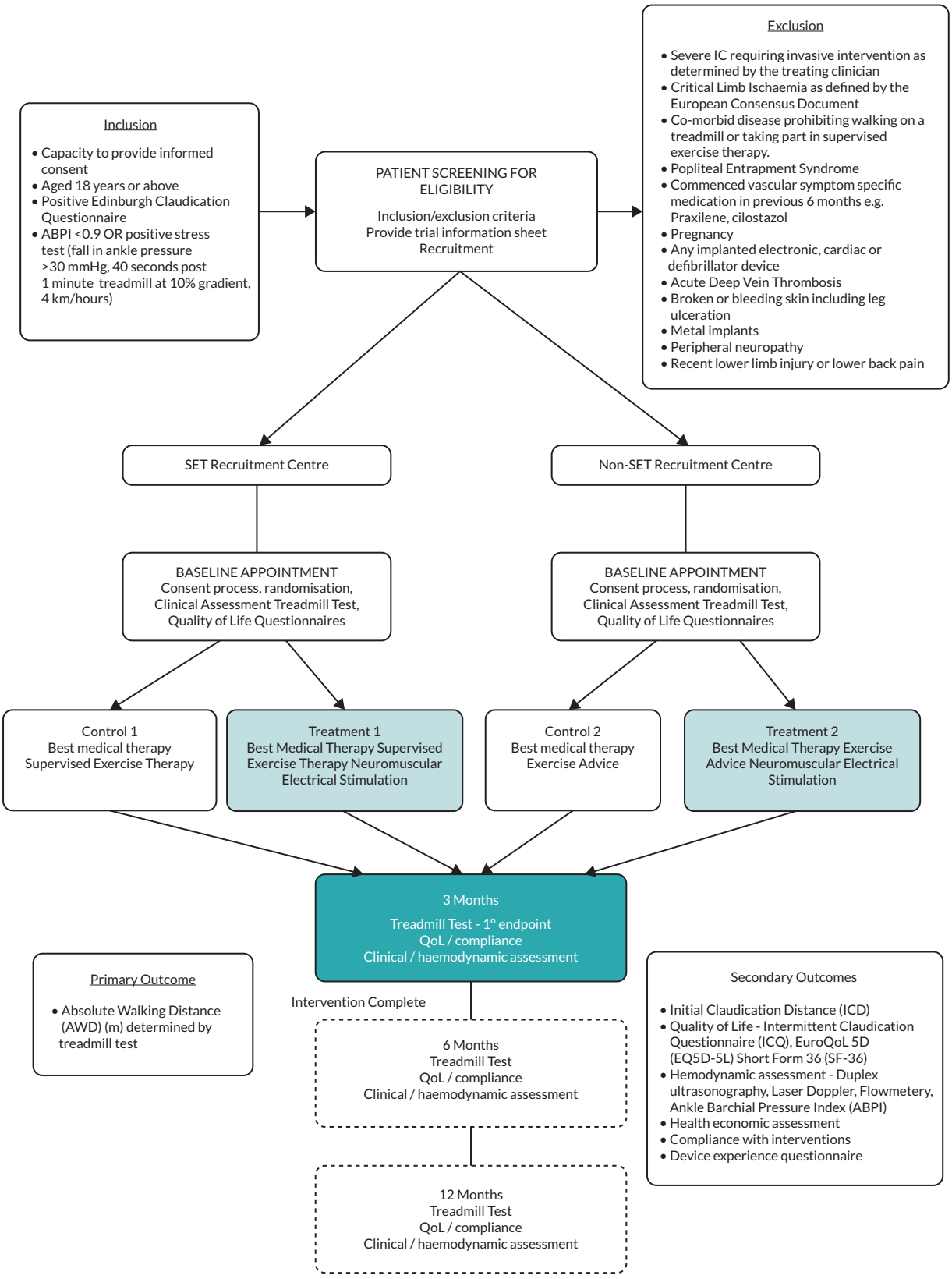
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Appendix 1 NESIC flow diagram



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