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

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## Disclosure of interests

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# Scientific summary

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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.

### *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

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.

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