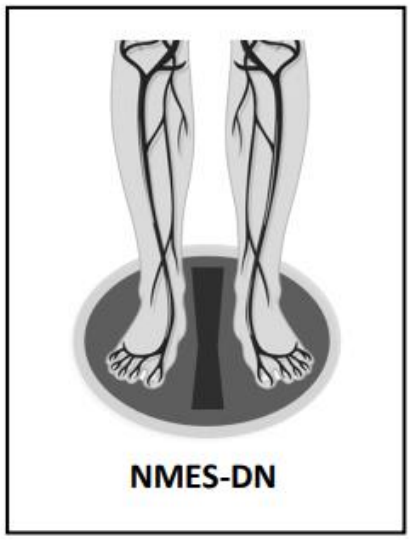
Neuromuscular Electrical Stimulation For The Treatment Of Diabetic Neuropathy: A Multi-centre, Double-blind, Pilot, Randomised, Sham-controlled Trial (NMES-DN)



Study Protocol

Version:	12.0
Date:	14 January 2025
Main Sponsor:	Imperial College London
Device Manufacturer:	Actegy Limited (Bracknell, UK)
Funder:	Actegy Limited (Bracknell, UK)
Study Coordination Centre:	Section of Vascular Surgery Department of Surgery and Cancer Imperial College London Charing Cross Hospital Fulham Palace Road London W6 8RF

RESEARCH REFERENCE NUMBERS

IRAS:	237312
REC Reference Number:	18/NE/0281
Sponsor Protocol Number:	18HH4610
ISRCTNregistry:	ISRCTN17050221
ClinicalTrials.gov Identifier:	NCT03767478 (https://clinicaltrials.gov/ct2/show/NCT03767478)

PROTOCOL AUTHORISATIONS

Separate protocol signature pages are provided at the end of this document for the Chief Investigator, Sponsor and Principal Investigator to sign. Protocol signature pages that have been signed will be filed in the Trial Master File (TMF).

REVISION SUMMARY

Protocol Version	Date	Revision Summary
V1.0 Draft – Not submitted to REC	07 November 2017	N/A – Original protocol
V2.0 Draft – Not submitted to REC	08 January 2018	- Primary outcome measure clarifications - Further details on statistical analyses and publication policy - Typographical corrections and clarifications throughout
V3.0 Draft – Not submitted to REC	20 March 2018	- Addition of co-investigator Professor Nick Oliver - Updated study design to RCT assessing three study arms including a sham device arm - Additional secondary outcome measures: DU, NTSS-6, NIS-LL, pain VAS - Included power calculation - Updated length of study to 24 months

		- Expanded on procedures and assessments - Typographical corrections and clarifications throughout
V4.0 Submitted to REC	20 March 2018	- Updated inclusion / exclusion criteria - Addition of MNSI as secondary outcome measure, removal of NIS-LL - Length of study amended to 18 months - Clarification of Imperial College data retainment policy - Typographical corrections and clarifications throughout
V5.0 Received REC favourable opinion	03 September 2018	Removal of data loggers to track device usage
V6.0 Received REC favourable opinion	24 September 2018	Name of NMES device changed from Revitive IX to Revitive Medic
V7.0 Received REC favourable opinion	24 September 2021	- Amended full and short title - Updated Contact List details - Addition of study statistician Dr Cain Clark - Change in study manager to Miss Sasha Smith - Updated background section with additional literature - Included Table of Contents, Abbreviations Glossary, Reference Diagram, Key Words, Study Summary and updated Appendices - Study objective details added - Summary table of objectives and outcomes added - Changed from single-site to a multi-centre, double-blinded RCT in the UK - Changed from a three arm to a two arm study design, removing

		Group B2 - Updated NMES device from Revitive Medic to Revitive Medic Coach with Revitive App - Randomisation strategy expanded upon - Blinding process added - Inclusion of tibial and superficial peroneal nerve for NCSs - Clarified diagnostic criteria for diabetes and DPN - Clarification of use of NTSS-6-SA (self-administered version) - Inclusion of monofilament test, cramping scale, DSIS, LDF, $TcPO_2$, ABPI and NMES sensation (intervention group only) assessments - Power and sample size calculation updated based on new study design and proposed statistical analyses - Addition of REDCap for randomisation and data storage - Incidental findings section added - Further details on consent, record keeping and data protection - Length of study amended to 21 months - Updated inclusion / exclusion criteria - Clarification of study visits including new assessments - Addition of text messaging service - Addition of therapy plan reminders before Week 10 and 20

		- Telephone call changed from Week 5 to Week 2 - Follow up visit changed from Month 12 to Month 9 - Additional details on assessment of safety - Details on data sharing updated - Inclusion of TMG - Typographical corrections and clarifications throughout
V8.0 Submitted to MHRA Received REC favourable opinion	03 May 2022	- Updated short title to NMES-DPN - Additional co-investigators - Updated Actegy Limited address - Updated Reference Diagram - Clarified MNSI as a separate outcome - Added Neuropathic Pain Symptom Inventory - Removed cramping questionnaire - Updated background literature and references - Changed randomisation service to Sealed Envelope - Added Quantitative Sensory Testing - Added credibility/ expectancy questionnaire - Included symptoms of DPN as part of inclusion criteria - Updated withdrawal criteria - Clarified timepoints for DU assessments - Added unmasking at final follow up visit - Safety reporting definitions and reporting updated, and to include MHRA

		- Provided further details on planned data analyses - Removed Coventry University as a data sharing collaborator - Patient and public involvement activities described - Typographical corrections and clarifications throughout
V9.0 Received no objection from MHRA Received REC favourable opinion	07 September 2022	- Updated study title and design to include pilot and sham-controlled trial - Changed diabetic peripheral neuropathy (DPN) to diabetic neuropathy (DN) throughout - Updated short title and study logo - Added following sections: Key Trial Contacts, Key Responsibilities, Primary Outcome Measure Hypotheses, Safety Outcome Measures, Study Setting, Monitoring, Amendments, Access To Data, Conflicts of Interest (to align with SPIRIT statement) - Updated Reference Diagram - Updated objectives and outcome measures to include assessment of feasibility and safety - Changed primary outcome measure to sural nerve only - Added Brief Illness Perception Questionnaire (Brief IPQ) - Removed DU, LDF and TcPO2 assessments - Changed NMES sensation to device sensation as will be recorded for both study groups - Updated background and literature with up-to-date evidence

		- Included further information on Randomisation Strategy and Blinding Process - Changed length of study to 18 months - Updated NCS criteria for diagnosis of DN - HIV test made optional - Clarified inclusion criteria: personal mobile phone required, and study smartphone provided - Amended exclusion criteria: used a NMES device within 1 year of randomisation - Updated Withdrawal Criteria - Added further information on Recruitment and Consent e.g. use of advertisements - Added section on Equality, Diversity and Inclusion - Removed unmasking at final visit - Added qualitative sub-study and analysis - Updated Patient and Public Involvement (PPI) Section - Included further information on planned data analyses such as primary outcome measure, feasibility outcome measures, safety outcome measures, secondary outcome measures and qualitative sub-study analyses - Included further information on study database - Updated sample size to 100 participants as a pilot study, provided justification - Included protocol signature pages

		- Typographical corrections and clarifications throughout
V10.0 Received no objection from MHRA Received REC favourable opinion	06 December 2023	- Addition of Trial Monitor - Removal of EQ-5D-5L questionnaire, Brief Illness Perceptions Questionnaire, Self-administered Neuropathy Total Symptom Score-6 and Ankle Brachial Pressure Index assessments - Addition of HBA1c blood test at baseline and Month 6 - Typographical corrections and clarifications throughout
V11.0 Received no objection from MHRA Received REC favourable opinion	05 August 2024	- Change of primary outcome measure to MNSI Part A questionnaire - Sural nerve conductivity moved to a secondary outcome - Participant retention rate also measured at 26 weeks - Change of treatment phase to 12 weeks and final follow up at 26 weeks - Change of study length to 22 months with 16 months recruitment and 6 months follow up - Removal of inclusion criterion: nerve conduction study of at least one lower limb must have a sural SNAP amplitude of <6 µV or absent - NCS and QST only performed for participants recruited at the central site - NCS does not need to be repeated at baseline if performed within 3 months of consent

		- Week 2 visit changed to Week 3 - Addition of Week 6 and Week 9 remote follow up visits - Addition of Total Symptom Score (TSS) - Removal of pain NRS and DSIS text messages - Removal of inclusion criterion to have a personal mobile phone to receive study text messages - Change in blinding process, whereby participants will be informed that this is a double-blind trial with a control arm and sham device - Typographical corrections and clarifications throughout
V12.0	14 January 2025	- Addition of Mr Darren Target to the statistical support team - Update to the Reference Diagram - Change of sample size to 64 - Clarification that the TSS is a 10-point rather than 11-point scale - Removal of control area assessment from QST - Update to the assessment of safety section to align with the current MHRA safety reporting procedures - Specification that the statistical software is SAS rather than R - Typographical corrections and clarifications throughout

KEY TRIAL CONTACTS

Chief Investigator:	**Professor Alun Davies** Professor of Vascular Surgery and Honorary Consultant Vascular Surgeon Section of Vascular Surgery Department of Surgery and Cancer Imperial College London Imperial Vascular Unit Imperial College Healthcare NHS Trust
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Main Protocol Contributors:	**Professor Alun Davies** **Miss Sasha Smith** **Mr Tristan Lane** **Dr Ian Mak** **Dr Cain Clark** **Professor John Norrie** **Professor Nick Oliver**
Statistical Support:	**Miss Sasha Smith** **Dr Cain Clark** **Professor John Norrie** **Mr Darren Target** Consultant Statistician Primoris Contract Solutions Ltd
Trial Management:	**Miss Sasha Smith**
Trial Monitor:	**Miss Jessica Barbut Siva**
Trial Management Group:	**Professor Alun Davies (Chair)**

	Miss Sasha Smith **Miss Jessica Barbut Siva** **Mr Tristan Lane** **Mr Ankur Thapar** **At least one member of the statistical support team** **At least one patient representative**
Patient Representatives:	**Ms Liz Piggot** Imperial College Healthcare NHS Trust **Ms Zoe Goodchild** Imperial College Healthcare NHS Trust
Sponsor:	**Imperial College London** is the main research sponsor for this trial. For further information regarding the sponsorship conditions, please contact the Head of Regulatory Compliance at: Research Governance and Integrity Team (RGIT) Address: Imperial College London and Imperial College Healthcare NHS Trust Room 215 Level 2 Medical School Building Norfolk Place London W2 1PG Tel: +44(0)207 594 1862 https://www.imperial.ac.uk/research-and-innovation/research-office/research-governance-and-integrity/
Funder:	**Actegy Limited** (Bracknell, UK) is the funder for this trial. For further information regarding funding, please contact Director Roseanna Penny: Address:

	1 Westpoint Western Road Bracknell Berkshire RG12 1HJ Email: roseanna.penny@actegy.com
Device Manufacturer:	**Actegy Limited** (Bracknell, UK) is the manufacturer of neuromuscular electrical stimulation (NMES) and sham devices for this trial and are supplying them free of charge. In addition to the study devices, they will be providing participants study smartphones free of charge. For further information regarding manufacturing of study devices and supplying study devices and smartphones, please contact Director Roseanna Penny: Address: 1 Westpoint Western Road Bracknell Berkshire RG12 1HJ Email: roseanna.penny@actegy.com
Other Vendors/Suppliers:	**Sealed Envelope Limited** (London, UK) will be providing the randomisation service. Tel: +44(0)203 488 5064 Address: Sealed Envelope Limited 501 Clerkenwell Workshops 27-31 Clerkenwell Close London EC1R 0AT **REDCap – Research Electronic Data Capture** (Tennessee, US) will be providing the internet-based database system. Imperial College London is a REDCap partner, and the database system will be built by the Trial Manager based at Imperial College London. Any queries should be directed to Trial Manager in the first instance: Tel: +44 (0)756 512 3056

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For **general queries**, supply of study documentation and data management, please contact:

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KEY RESPONSIBILITIES

Imperial College London are responsible for:

- Sponsoring the trial in accordance with the Medicines for Human Use (Clinical Trial) Regulations 2004, UK Policy Framework for Health and Social Care Research principles and other regulatory requirements as appropriate
- Providing insurance or indemnity arrangements for negligent and non-negligent harm to clinical trial subjects
- Storing study devices in appropriate conditions
- Securing contracts for the supply of resources other than study devices
- Designing and writing the protocol in compliance with Medicines for Human Use (Clinical Trial) Regulations 2004, Good Clinical Practice (GCP) principles, ISO 14155:2020 standards, and other regulatory requirements as appropriate, also considering the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 Statement
- Managing and conducting the research in compliance with the protocol, Medicines for Human Use (Clinical Trial) Regulations 2004, UK Policy Framework for Health and Social Care Research principles, GCP principles, ISO 14155:2020 standards, Data Protection Act and other regulatory requirements as appropriate
- Preparing and submitting materials for Clinical Trial Authorisation (together with Actegy Limited) and to relevant ethics committees and NHS organisations
- Preparing and submitting proposed substantial amendments of the protocol to the regulatory authorities, relevant ethics committees and NHS organisations
- Creating and maintaining the Trial Master File (TMF)
- Maintaining detailed records of all Adverse Events (AEs) as specified in the protocol, and report AEs in accordance with legal and regulatory requirements
- Ensuring that Serious Adverse Events (SAEs) are reviewed by appropriate committees/authorities for the monitoring of trial safety
- Ensuring that all Suspected Unexpected Serious Adverse Reactions (SUSARs) are identified and fully reported to the regulatory authorities and relevant ethics committees within the required timelines
- Ensuring that investigators are aware of any SUSARs occurring in relation to the study device
- Analysing trial data, or ensure this is performed by an appropriate collaborator

- Initiating and coordinating review and submission of abstracts, posters and publications
- Archiving all clinical trial records on conclusion of the clinical trial

Actegy Limited are responsible for:

- Manufacturing, packaging and labelling the study devices in accordance with Medicines for Human Use (Clinical Trial) Regulations 2004, ISO 14155:2020 standards and Good Manufacturing Practice principles
- Providing insurance or indemnity arrangements for manufacture of study devices
- Storing study devices in appropriate conditions
- Preparing and submitting materials for Clinical Trial Authorisation (together with Imperial College London)
- Recalling of study devices
- Providing funding for the clinical trial

The Trial Management Group are responsible for:

- Having oversight of trial set-up and day-to-day management of the trial
- Ensuring that the trial is conducted at all times to the standards set out in regulatory requirements and GCP principles
- Ensuring the rights, safety and well-being of the trial participants are not compromised
- Reviewing and approving the study protocol/other study paperwork and subsequent amendments or administrative changes to the protocol/other study paperwork as applicable
- Ensuring that the study protocol and any subsequent amendments are adhered to
- Reviewing study progress and address any problems or issues that arise regarding the conduct of the trial
- Promoting the trial
- Defining the contents and schedule of the trial report
- Interpreting the results of the trial
- Reviewing and approving any trial publications

Please see **7.2 SAFETY RESPONSIBILITIES** for detailed safety responsibilities.

This protocol describes the NMES-DN trial and provides information about procedures for entering participants. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to

investigators in the study. Problems relating to this study should be referred, in the first instance, to the Chief Investigator (CI).

GLOSSARY OF ABBREVIATIONS

AC/DC	Alternating Current / Direct Current
ADE	Adverse Device Effect
AE	Adverse Event
ANCOVA	Analysis of Covariance
ASADE	Anticipated Serious Adverse Device Effect
BBS	Berg Balance Scale
CI	Chief Investigator
CMAP	Compound Muscle Action Potential
Conmeds	Concomitant Medications
COREQ	Consolidated criteria for reporting qualitative research
CRF	Case Report Form
DFNS	German Research Network on Neuropathic Pain
DFU	Diabetic Foot Ulcer
DN	Diabetic Neuropathy
DSIS	Daily Sleep Interference Scale
DU	Duplex Ultrasonography
DVT	Deep Vein Thrombosis
eCRF	Electronic Case Report Form
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GP	General Practitioner
HbA1c	Glycated haemoglobin
HIV	Human Immunodeficiency Virus
HRA	Health Research Authority
IB	Investigator's Brochure
IFU	Instructions For Use
ITT	Intention To Treat
LDF	Laser Doppler Flowmetry
MAR	Missing At Random
MedDRA	Medical Dictionary for Regulatory Activities
MNSI	Michigan Neuropathy Screening Instrument
NCS	Nerve Conduction Study
NHS	National Health Service

NIS-LL	Neuropathy Impairment Score in the Lower Limbs
NMES	Neuromuscular Electrical Stimulation
NPSI	Neuropathic Pain Symptom Inventory
NRS	Numerical Rating Scale
PI	Principal Investigator
PIC	Participant Identification Centre
PP	Per Protocol
PPI	Patient and Public Involvement
QoL	Quality of Life
QST	Quantitative Sensory Testing
RCT	Randomised Controlled Trial
R&D	Research and Development
REC	Research Ethics Committee
REDCap	Research Electronic Data Capture Software
RGIT	Research Governance and Integrity Team
RIN	Revitive Identification Number
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SEP	Supervised Exercise Programme
SFA	Superficial Femoral Artery
SIV	Site Initiation Visit
SNAP	Sensory Nerve Action Potential
SOP	Standard Operating Procedure
SPIRIT	Standard Protocol Items: Recommendations for Interventional Trials
TAMV	Time-Averaged Mean Velocity
$TcPO_2$	Transcutaneous Pressure of Oxygen
TMF	Trial Master File
TMG	Trial Management Group
TSS	Total Symptom Score
UK	United Kingdom
US	United States
USADE	Unanticipated Serious Adverse Device Effect
VAS	Visual Analogue Scale

WHO	World Health Organisation

KEYWORDS

Diabetes, diabetic neuropathy, distal symmetrical polyneuropathy, nerve conductivity, nerve conduction study, neuromuscular electrical stimulation

REFERENCE DIAGRAM

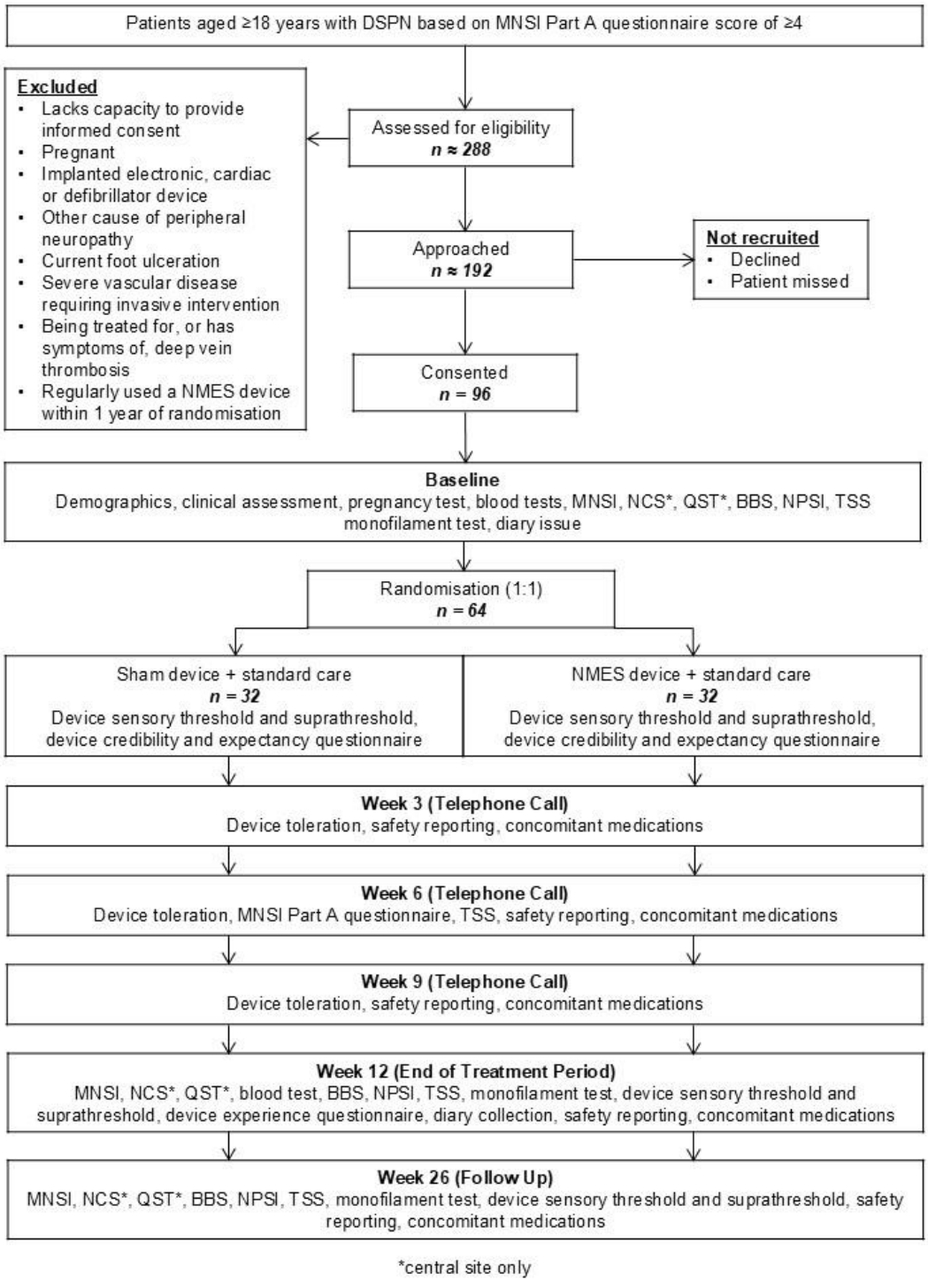


Figure 1: Flowchart of NMES-DN trial presenting planned recruitment and follow up

STUDY SUMMARY

TITLE Neuromuscular Electrical Stimulation For The Treatment Of Diabetic Neuropathy: A Multi-centre, Double-blind, Pilot, Randomised, Sham-controlled Trial (NMES-DN)

DESIGN Multi-centre, Double-blinded, Pilot, Randomised (1:1), Sham-controlled Trial

AIMS To assess the potential efficacy signal, feasibility and safety of a NMES device compared to a sham device as an adjunct to local standard of care in patients with DN

OUTCOME MEASURES

Primary outcome measure:

- Neuropathy symptoms – measured using the Michigan Neuropathy Screening Instrument (MNSI) Part A questionnaire at 12 weeks

Feasibility outcome measures:

- Recruitment rate measured using screening and randomisation logs, participant retention rate measured using randomisation and withdrawal logs and treatment adherence rate measured using Revitive App and patient diary

Safety outcome measures:

- Adverse Events (AEs), Adverse Device Effects (ADEs), Serious Adverse Events (SAEs) and Serious Adverse Device Effects (SADEs) measured using AE and SAE forms

Secondary outcome measures:

- Sural, superficial peroneal, common peroneal and tibial nerve conductivity measured using a nerve conduction study (NCS)
- Somatosensory nerve fibre function – measured using Quantitative Sensory Testing (QST)
- Blood glucose – measured using HbA1c
- Mobility and balance – measured using Berg Balance Scale (BBS)
- Neuropathy signs– measured using the Michigan Neuropathy Screening Instrument (MNSI) Part B examination
- Symptoms – measured using Total Symptom Score (TSS) covering paraesthesia, pain, numbness, cramp and sleep disruption on a 10-point Numerical Rating Scale (NRS)
- Protected sensation – measured using monofilament test
- Pain – measured using Neuropathic Pain Symptom Inventory (NPSI)
- Device sensation – measured using device sensory threshold and suprathreshold
- Device credibility and expectancy – measured using modified credibility and expectancy questionnaire
- Device experience – measured using questionnaire

ELIGIBILITY

Inclusion

- ≥18 years or older (no upper age limit)
- Diagnosis of either type 1 or type 2 diabetes
- Diagnosis of DN based on ≥4 MNSI questionnaire score and blood testing
- Access to internet at home to use the Revitive App (study smartphone provided)

Exclusion

- Lacks capacity to provide informed consent
- Pregnant
- Implanted electronic, cardiac or defibrillator device
- Other cause of peripheral neuropathy
- Current foot ulceration
- Severe vascular disease requiring invasive intervention
- Being treated for, or has symptoms of Deep Vein Thrombosis (DVT)
- Regularly used a NMES device within 1 year of randomisation

LENGTH OF STUDY 22 months: 16 months recruitment and 6 months follow up (end of treatment phase is at 3 months; end of follow up is at 6 months).

TABLE OF CONTENTS

1. INTRODUCTION

1.1 BACKGROUND

1.1.1 DIABETES AND DIABETIC NEUROPATHY

Diabetes is a major global healthcare problem. Approximately half a billion people are estimated to have diabetes worldwide, and this is forecasted to rise to 700 million by 2045 (1). In the United Kingdom (UK), an estimated 4.6 million people have diabetes, and this is predicted to rise to 5 million people by 2025. In addition, it is estimated that 1 million cases of type 2 diabetes in the UK are currently undiagnosed (2).

Diabetes is a chronic metabolic condition characterised by hyperglycaemia, which damages blood vessels and leads to macrovascular (coronary artery disease, cerebrovascular disease and peripheral arterial disease) and microvascular (nephropathy, retinopathy and neuropathy) complications. The most prevalent complication of diabetes, diabetic neuropathy (DN), affects more than 50% of people with diabetes (3,4). Distal symmetrical polyneuropathy is the most common type of DN, with symptoms ranging from numbness to burning, prickling, aching, tightness and hypersensitivity in the distal extremities.

The insensate lower limb increases the risk of developing diabetic foot ulcers (DFUs). Up to a quarter of people with diabetes will be affected by DFUs (4,5). DFUs are particularly challenging to manage when the cause is neuropathic or neuro-ischemic, because numbness in the lower limb can cause patients to walk on infected wounds without realising it (4,6). DFUs are also associated with high mortality rates, which rise even further after major lower limb amputation (4,7,8). The associated economic burden of DFUs is also high, with the cost to the National Health Service (NHS) in the UK estimated at £1 billion per year (4,9).

Guidelines for the management of DN emphasise improved glycaemic control, lifestyle modifications, footcare and pain management, however these strategies are sub-optimal. For example, glycaemic control significantly reduces the risk of DN in people with type 1 diabetes but not in people with type 2 diabetes (4,10). Pain management focuses on pharmacotherapies such as anticonvulsants and selective serotonin reuptake inhibitors, but these medications have a variety of side effects and are often only effective in the short term (11). Furthermore, only approximately 30% of people with DN experience pain, therefore the strategies for people who experience numbness are even more limited (3,4).

Exercise is a promising lifestyle modification for the prevention and treatment

of DN, with a moderate level of evidence (4). A recent meta-analysis (13 RCTs, 592 participants) concluded that exercise programmes can improve mobility, peripheral nerve conductivity and glycaemic control in people with DN (4,12). Although exercise appears to be an effective intervention, more robustly designed, large-scale randomised controlled trials (RCTs) are needed to strengthen its evidence base (4,11). Other challenges of exercise interventions include adherence, under-resourced services to provide supervised exercise programmes (SEPs) and long-term behaviour change (4).

The pathogenesis of DN is poorly understood, which has slowed the development of novel disease-modifying therapies. However, it is widely accepted that DN is characterised by peripheral nerve fibre and microvessel dysfunction, which is primarily caused by hyperglycaemia and other metabolic factors such as hyperlipidaemia and impaired insulin signalling (13). As a result, it is critical to conduct research into interventions that address both peripheral nerve fibre and circulatory dysfunction.

1.1.2 NEUROMUSCULAR ELECTRICAL STIMULATION

Neuromuscular electrical stimulation (NMES) is the application of electrical impulses which are of sufficient intensity to produce artificial contraction of muscle tissue. NMES is commonly applied at the lower limb via transcutaneous electrodes to evoke calf and thigh muscle contraction. The muscle contraction simulates exercise and has been shown to increase blood flow in healthy individuals (14,15) and in patients with vascular disease (16–18). It has also been utilised to accelerate recovery after orthopaedic surgery, stroke and intensive care stay (19–21).

There is a growing body of clinical evidence to support the use of NMES in improving circulation. An unpublished randomised, repeated measures, controlled study (n=16) demonstrated that peripheral blood flux was significantly enhanced at the foot by 8-fold and at the calf by 5-fold whilst using a NMES device compared to resting. Whereas the increase during voluntary exercise was 3-fold and 2-fold at the foot and calf, respectively ($p<0.008$). Compared to voluntary exercise, NMES also elicited a greater increase in tissue oxygenation at the foot ($p<0.018$) (14).

A separate study, investigating the same type of NMES device, showed that both venous and arterial haemodynamic parameters significantly increased (venous blood flow $p=0.014$; venous time-averaged mean velocity [TAMV] $p=0.065$; arterial blood flow $p<0.0001$; arterial TAMV $p=0.0003$) in healthy individuals during NMES device use compared to baseline. Furthermore,

improvement was also sustained shortly after device cessation, though this was not significant (15).

Improvement in blood flow whilst using a NMES device has been observed in patients with peripheral arterial disease. A pilot and subsequent RCT reported that participants randomised to a 6-week therapy plan of one 30-minute NMES session per day plus a SEP were able to walk for significantly longer without pain (initial claudication distance – 46% increase; p=0.014) and walk for significantly longer without stopping due to pain (maximum claudication distance – 46% increase; p<0.001) compared to those randomised to a SEP alone (17).

A similar 6-week NMES therapy plan has also been trialled in patients with chronic venous insufficiency. In this study, those randomised to the control group received a sham device. There were significant differences in venous blood flow between the active NMES and sham groups after 6 weeks (p<0.0001) (16). A more recent study, comparing groups allocated to 30 minutes and 60 minutes of NMES per day and no NMES (control) also recorded significant differences in venous haemodynamic parameters, microcirculatory flow and foot temperature after 6 weeks (p<0.001) (18).

1.1.3 RISKS

The risks are defined in the **Instructions for Use (IFU)** and **Investigators Brochure (IB).**

1.1.4 BENEFITS

The NMES device may improve neuropathy symptoms in patients with DN, and therefore have an adjuvant benefit when provided in addition to standard of care. It may also improve other clinical and subjective outcomes which include, but are not limited to, sural, superficial peroneal, common peroneal and tibial nerve conductivity, somatosensory nerve fibre function, blood glucose, mobility and balance, neuropathy signs and symptoms, protected sensation.

1.1.5 RATIONALE FOR STUDY

NMES is hypothesised to improve neuropathy symptoms in people with DN by directly stimulating peripheral nerves and increasing circulation in the lower limbs. Findings from a proof-of-concept study of NMES in people with DN showed that Michigan Neuropathy Screening Instrument (MNSI) Part A questionnaire scores significantly improved from baseline after 10 weeks of daily NMES device use (p<0.028) (22). To further understand the effects of this intervention in people with DN, more high-quality research is needed.

Hence, this pilot, randomised, sham-controlled trial is planned to robustly assess the potential efficacy signal, feasibility and safety of a NMES device as an adjunct to standard of care in people with DN. The inclusion of a sham control also allows for the assessment of any sham treatment effects.

If this pilot RCT demonstrates a potential efficacy signal and the NMES device is deemed safe, future plans are to run a statistically powered, multi-centre, RCT. If clinical efficacy and safety are demonstrated in larger trials, this could lead to an accessible, non-invasive, safe and effective treatment option for patients with DN and may reduce the burden to patients and healthcare systems.

Details of the NMES device used in this study (Revitive Medic Coach, Actegy Ltd, Bracknell, UK) are described below in section **3.1 TREATMENT REGIMENS** and are described in the **Instructions For Use (IFU)** and **Investigator's Brochure (IB).**

For further details on the justification of the trial please see the **Clinical Investigation Decision** document.

2. STUDY OBJECTIVES AND OUTCOME MEASURES

2.1 PRIMARY OBJECTIVES

The primary objectives are to assess the potential efficacy signal, feasibility and safety of a NMES device as an adjunct to standard of care in people with DN.

The potential efficacy signal of a NMES device as an adjunct to standard of care will be primarily assessed by a change in neuropathy symptoms from baseline to the end of the treatment phase (12 weeks), compared to a sham device as an adjunct to standard of care. Neuropathy symptoms will be measured using the MNSI and will also be evaluated at follow up 6 weeks and 26 weeks, but the end of the treatment phase (12 weeks) will be the primary timepoint of interest.

The feasibility of a NMES device as an adjunct to standard of care will be assessed through recruitment rate, which will compare number of patients pre-screened/identified and number of participants recruited at baseline, participant retention rate, which will compare number of participants randomised and number of participants on study at the end of the treatment phase (12 weeks) and follow up (26 weeks), and adherence to treatment at the end of the treatment phase (12 weeks), which will be measured through the Revitive App and a patient diary.

The safety of a NMES device as an adjunct to standard of care will be assessed through reporting of Adverse Events (AEs), Adverse Device Effects (ADEs), Serious Adverse Events (SAEs) and Serious Adverse Device Effects (SADEs). For further details of assessment of safety and definitions please see **7. ASSESSMENT OF SAFETY**.

2.2 SECONDARY OBJECTIVES

The secondary objectives are to determine if there are changes in other clinical and subjective outcomes when using a NMES device as an adjunct to standard of care in people with DN.

Other clinical and subjective outcomes include, but are not limited to, sural, superficial peroneal, common peroneal and tibial nerve conductivity, somatosensory nerve fibre function, mobility and balance, neuropathy signs and symptoms, protective sensation, neuropathic pain and device sensation. Changes in these outcomes from baseline to the end of the treatment phase (12 weeks) and follow up (26 weeks) will be compared to a sham device as an adjunct to standard of care. In addition, blood glucose will be compared from baseline to the end of the treatment phase (12 weeks). Participants' views on device credibility and expectancy will be compared after their first treatment session at baseline and their experiences of the study device will be compared at the end of the treatment phase (12 weeks).

2.3 PRIMARY OUTCOME MEASURE

The primary outcome is neuropathy symptoms measured using the MNSI Part A questionnaire at 12 weeks. The MNSI Part A is a validated screening questionnaire for DN, consisting of 15 yes or no questions about lower limb sensation. The total score is based on 13 questions, as two questions are excluded from the scoring (23,24).

2.4 PRIMARY OUTCOME MEASURE HYPOTHESES

Primary outcome null hypothesis (H_0): There is no statistically significant difference in change in neuropathy symptoms measured using the MNSI Part A questionnaire total score between the control and intervention groups from baseline to the end of the treatment phase (12 weeks).

Primary outcome alternative hypothesis (H_1): There is a statistically significant difference in change in neuropathy symptoms measured using the MNSI Part A questionnaire total score, between the control and intervention groups from baseline to the end of the treatment phase (12 weeks).

2.5 FEASIBILITY OUTCOME MEASURES

- Recruitment rate – measured using screening and randomisation logs
- Participant retention rate – measured using randomisation and withdrawal logs
- Adherence to treatment – measured using Revitive App and a patient diary

2.6 SAFETY OUTCOME MEASURES

- Adverse Events (AEs) – collected and reported via AE form
- Adverse Device Effects (ADEs) – collected and reported via AE form
- Serious Adverse Events (SAEs) – collected and reported via SAE form
- Serious Adverse Device Effects (SADEs) – collected and reported via SAE form

2.7 SECONDARY OUTCOME MEASURES

- Sural nerve conductivity – measured using a nerve conduction study (NCS), includes conduction velocity (m/s), calculated using distance and latency (ms), and SNAP amplitude (μV) **(central site only)**
- Superficial peroneal nerve conductivity – measured using a NCS, includes conduction velocity (m/s), calculated using distance and latency (ms), and SNAP amplitude (μV) **(central site only)**
- Common peroneal nerve conductivity **–** measured using a NCS, includes conduction velocity (m/s), calculated using distance and distal latency (ms), Compound Muscle Action Potential (CMAP) amplitude (mV) and minimum F wave latency (ms) **(central site only)**
- Tibial nerve conductivity – measured using a NCS, includes conduction velocity (m/s), calculated using distance and distal latency (ms), CMAP amplitude (mV) and minimum F wave latency (ms) **(central site only)**
- Somatosensory nerve fibre function – measured using Quantitative Sensory Testing (QST) **(central site only)**
- Blood glucose – measured using HbA1c
- Mobility and balance – measured using validated Berg Balance Scale (BBS) (25)
- Neuropathy signs – measured using the validated MNSI Part B physical examination (23,24)
- Protected sensation – measured using monofilament test
- Symptoms – measured using Total Symptom Score (TSS) covering paraesthesia, pain, numbness, cramp and sleep disruption on a 10-point Numerical Rating Scale (NRS)
- Neuropathic pain – measured using Neuropathic Pain Symptom Inventory (NPSI) (26)

- Device sensation – measured using device sensory threshold and suprathreshold
- Device experience – measured using device experience questionnaire
- Device credibility and expectancy – measured using modified credibility and expectancy questionnaire (27)

Timepoints at which primary, feasibility, safety and secondary outcome measures are assessed are included in **Table 1**.

Table 1: Summary of objectives and outcomes

Objectives	Outcome measure	Measuring tool	Timepoint(s) of evaluation of this outcome
Primary objectives	Neuropathy symptoms (Primary)	MNSI Part A questionnaire	Week 6, Week 12 (Primary), Week 26
	Recruitment rate (Feasibility)	Screening logs and randomisation logs	Pre-screening / Identification, Recruitment and Consent, Baseline
	Participant retention rate (Feasibility)	Randomisation logs and withdrawal logs	Recruitment and Consent, Baseline, Week 12, Week 26
	Adherence to treatment (Feasibility)	Revitive App and a patient diary	Week 12
	Adverse Events (Safety)	AE form	Baseline, Week 3, Week 6, Week 9, Week 12, Week 26 (and any communication in between)

	Adverse Device Effects (Safety)	AE form	Baseline, Week 3, Week 6, Week 9, Week 12, Week 26 (and any communication in between)
	Serious Adverse Events (Safety)	SAE form	Baseline, Week 3, Week 6, Week 9, Week 12, Week 26 (and any communication in between)
	Serious Adverse Device Effects (Safety)	SAE form	Baseline, Week 3, Week 6, Week 9, Week 12, Week 26 (and any communication in between)
Secondary objectives	Sural nerve conductivity **(Central site only)**	NCS	Week 12, Week 26
	Superficial peroneal nerve conductivity **(Central site only)**	NCS	Week 12, Week 26
	Common peroneal nerve conductivity **(Central site only)**	NCS	Week 12, Week 26
	Tibial nerve conductivity **(Central site only)**	NCS	Week 12, Week 26
	Somatosensory nerve fibre function **(Central site only)**	QST	Week 12, Week 26
	Blood glucose	HbA1c	Week 12
	Mobility and balance	BBS	Week 12, Week 26
	Neuropathy signs	MNSI Part B Questionnaire	Week 12, Week 26

	Symptoms	TSS	Week 6, Week 12, Week 26
	Protected sensation	Monofilament test	Week 12, Week 26
	Neuropathic pain	NPSI	Week 12, Week 26
	Device sensation	Device sensory threshold and suprathreshold	Week 12, Week 26
	Device credibility and expectancy	Modified credibility and expectancy questionnaire	Baseline
	Device experience	Questionnaire	Week 12

3. STUDY DESIGN

3.1 TREATMENT REGIMENS

This is a multi-centre, double-blind, pilot, randomised (1:1), sham-controlled trial assessing two arms:

Arm 1 (Control group):	Sham Device + Standard of Care
Arm 2 (Intervention group):	NMES Device + Standard of care

3.1.1 STANDARD OF CARE

Standard of care is defined as the therapy for DN available locally to the clinical trial site. It can comprise of advice on glycaemic control, footcare, anticonvulsant and antidepressant medications. For pragmatism, standard of care will be as per local guidelines and is not standardised by the study protocol. A full medical and drug history will be taken at baseline and concomitant medications will be recorded and monitored at each study visit. There are no prohibited concomitant medications for this trial.

3.1.2 NEUROMUSCULAR ELECTRICAL STIMULATION DEVICE (INTERVENTION)

Revitive Medic Coach (Figure 2) is a CE Marked, Class IIa, NMES medical device. It is intended to deliver nerve and muscle stimulation of the legs, feet and ankles to actively improve circulation. It is suitable for healthy individuals or people with poor circulation, a sedentary lifestyle, limited mobility, following

surgery or injury and those with diabetes (including DN), osteoarthritis, peripheral arterial disease, chronic venous insufficiency and chronic obstructive pulmonary disease. The intended operator profile is based on users in the home environment.

The device causes nerve and muscle stimulation by applying electrical stimulation to the feet via large conductive rubber footpad electrodes. It is accompanied by a CE Marked Class II AC/DC power adaptor (Figure 2) for charging and once sufficiently charged can be cordless for use. Routinely, it is also accompanied with electrode body pads, but these will not be provided for this study. The device can be activated via the power on/off button on the device or by the Revitive App via Bluetooth pairing, which is available for download from Play or App stores. For the purposes of this study, participants will be provided with a study smartphone to access the Revitive App. The device includes hydration sensors, which provide feedback to the user if they are required to hydrate their feet to improve conductivity. It also has an IsoRocker function, which allows natural heel toe raises and accentuates the calf muscle pump action at the ankle.

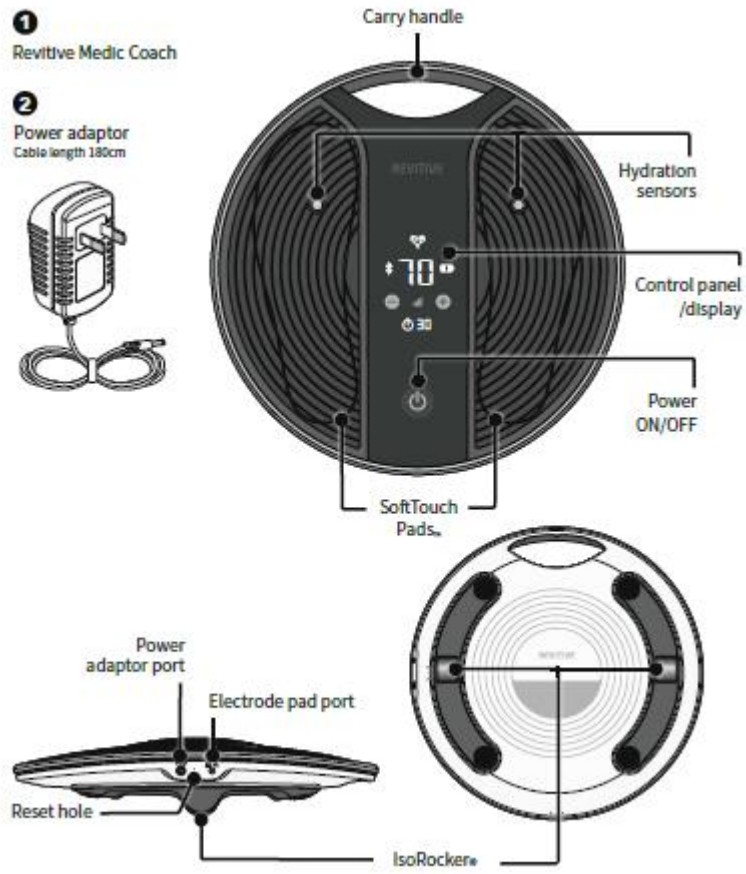
The key device components that are intended to come into contact with the human body are the silicone rubber footplates. The device comes into non-invasive contact with the user's intact skin on the plantar surface, via the footplate electrodes. These are comprised of Silicone (ER-70 + Carbon Nanotube) rubber. Transient contact may also be made in carrying the device, plugging in the charging cables or in using the device display interface.

The device is programmed with the Standard Programme, constructed from 15 one-minute low frequency waveforms patterns that repeat twice in each 30-minute programme. The intensity of electrical stimulus can be varied from level 0 to 99. When first using the NMES device at the baseline visit, baseline device sensory and motor thresholds will be established for participants by systematically increasing the stimulation intensity in increments of one whilst the participant provides verbal sensory feedback. The minimal intensity, at which the participant is able to clearly feel electrical stimulation, will be recorded as the sensory threshold; and that producing visible muscle twitches of the medial gastrocnemius will be the motor threshold. The stimulation intensity will be adjusted to produce visible but non-painful contraction of the lower limb musculature at twice the individual motor threshold or as much as the participant can tolerate as comfortable (suprathreshold) and this will be recorded. Participants may not perceive any sensation or muscle contractions because of their diabetic neuropathy (a disease characterised by sensorimotor dysfunction). In this case, participants should be encouraged to use the device at the highest stimulation intensity (level 99), provided there

are no other concerns with using the device at this level. Device sensory threshold and suprathreshold will also be recorded at Week 12 and Week 26 to assess any change in participants' device sensation over time. At baseline, an IFU will be given to all participants so they can use their study device at home. At Week 3, Week 6 and Week 9 participants will be contacted to see how they are tolerating their study device. During this visit and across the treatment phase, the clinical judgement of the local Principal Investigator (PI) will determine whether a participant is experiencing problems that require reducing the stimulation intensity level or stopping treatment.

Further details on the NMES device can be found in in the **Instructions for Use (IFU)** and **Investigator's Brochure (IB).**

Figure 2: Revitive Medic Coach and power adaptor



3.1.3 SHAM DEVICE (CONTROL)

A sham control device has been included for the assessment of any sham treatment effects. The sham device will be a modified Revitive Medic Coach with all external appearances the same but with a maximum voltage cap to provide only very low sensory stimulation. It will begin at an intensity level of 5 for the first minute then level 2 for the second minute, then to a level zero for the remaining session. The numbers on the sham device and the Revitive App will display at the corrected intensity, similar to the display units on the NMES device to prevent unblinding. As the sham device still produces some stimulation, albeit very low, it is possible that there may be a change in sural nerve conductivity in the control group.

The same procedure as for the intervention group will be followed in that participants will be familiarised with their allocated study device and be provided with a study smartphone. Device sensory and suprathresholds will be established at baseline and recorded at Week 12 and Week 26 to assess any change in participants' device sensation over time. Participants may not perceive any sensation or muscle contractions because the sham device produces very low stimulation and/or because of their diabetic neuropathy (a disease characterised by sensorimotor dysfunction). In this case, participants should be encouraged to use the device at the highest stimulation intensity (level 99), provided there are no other concerns with using the device at this level.

At baseline, an IFU will be given to all participants so they can use their study device at home. At Week 3, Week 6 and Week 9 participants will be contacted to see how they are tolerating their study device.

Further details on the sham device can be found in in the **Instructions for Use (IFU)** and **Investigator's Brochure (IB).**

3.1.4 TREATMENT PHASE

For the purpose of the trial, all participants will be asked to use their allocated study device for two 30-minute sessions per day, a minimum of five hours per week for 12 weeks at suprathreshold (twice the individual motor threshold or as much as the participant can tolerate as comfortable). If participants do not perceive any sensation or muscle contractions, they should be encouraged to use their study device at the highest stimulation intensity (level 99), provided there are no other concerns with using the device at this level. The maximum total treatment time of 3 hours per day will be advised to minimise the potential for muscle fatigue. Adherence to treatment will be recorded in a patient diary and collected via the Revitive App. Participants will also receive

reminders to complete their treatment sessions via the Revitive App. Study smartphones will be provided for participants to access the Revitive App.

3.1.5 STUDY DEVICE ACCOUNTABILITY

During the clinical trial, the study devices will be fully traceable due to individually assigned device codes. Access to study devices will be restricted to authorised persons only and appropriate records will be kept by the device manufacturer, study coordination centre and clinical trials sites to document the physical location of all study devices from shipment from the device manufacturer to the clinical trial sites, provided to participants for the clinical trial period (12 weeks), returned to the clinical trial site and then provided to participants to keep at the end of the trial. Records will be kept of who received, used, returned or disposed (if applicable) of the study devices.

3.2 RANDOMISATION STRATEGY

Participants will be randomised in a 1:1 design, intervention: control at baseline to the following groups:

1. Sham Device + Standard of Care (Control group)
2. NMES Device + Standard of care (Intervention group)

The online computer software application Sealed Envelope (London, UK) will be used for randomisation, and it will be programmed with a randomisation schedule blocked with random block sizes. To ensure concealment, the block sizes will not be revealed until the analysis stage (after last patient last visit).

Randomisation and study assessments must be performed by a blinded researcher. The blinded researcher will confirm the eligibility criteria that must be met to allow randomisation on the online service. Once confirmed, Sealed Envelope will provide a study device code rather than treatment allocation. The unblinded randomisation list ‘code-break’ for treatment allocation will remain concealed from the study team and be held by the device manufacturer and an unblinded researcher at the study coordination centre who will not interact with participants.

There will be no randomisation within sites because ‘there are only two clinical trial sites planned, with the majority of recruitment expected to take place at Imperial College Healthcare NHS Trust. This is also consistent with Food and Drug Administration (FDA) Good Review Practice guidance, which suggests that stratification by centre is not feasible for multi-centre trials with small numbers recruited per site (28).

3.3 BLINDING PROCESS

As this is a double-blind study, both participants and researchers (including

outcome assessors) will be blinded to treatment allocation. Participants will be aware it is a double-blind study, in that there is a 50% chance they will be randomised to a sham device. At the study coordination centre, there will be an unblinded researcher who will not interact with patients. The unblinded randomisation list 'code-break' will only be accessible to the device manufacturer and unblinded researcher.

Participants may not perceive any sensation or muscle contractions because the sham device produces very low stimulation and/or because of their diabetic neuropathy (a disease characterised by sensorimotor dysfunction). Participants in the active NMES arm may also not perceive any sensation or muscle contractions because of their diabetic neuropathy.

During the course of a trial, unblinding should only occur if it is relevant to the safety and medical management of the participant. The final decision of unblinding will rest with the treating clinician. Ideally, where time allows, there should be a discussion with the Chief Investigator (CI) about the need to unblind; if this is not an option, the PI should notify the CI as soon as possible afterwards. The unblinded researcher at the study coordination centre will only share the treatment allocation details of the participant required to be unblinded, the full unblinded randomisation list 'code-break' will still be concealed from the study team. Every effort should be made to limit sharing treatment allocation details to the treating clinician and not to divulge this to the study team, PI (unless treating clinician) and CI.

All requests for unblinding should be documented including details of who made the request, who performed it, how it was carried out and the reason. The treatment allocation should not be included on this documentation as it could unblind further members of the clinical trial site team. The local PI is responsible for ensuring that the documentation is completed, a copy is filed in the Investigator Site File, and a copy is sent to the Trial Manager/Monitor for filing in the TMF. A record should also be made in the participant's medical notes, case report form (CRF) and electronic Case Report Form (eCRF) to document the unblinding.

3.4 STUDY SETTING

This study is open to all patients at the participating NHS sites (Table 2) meeting specific inclusion and exclusion criteria.

Table 2: Clinical trial sites

Number	Principal Investigator	Address	Institution	Country
1.	Professor Alun Davies	Charing Cross Hospital Fulham Palace Road London W6 8RF	Imperial College Healthcare NHS Trust	UK
2.	Mr Ankur Thapur	Basildon and Thurrock University Hospital Essex SS16 5NL	Mid and South Essex NHS Foundation Trust	UK

These clinical trial sites have been selected because the local PIs have indicated the trial is feasible and that they have the capacity and capability to conduct the trial at their site. In addition to clinical trial sites, potential participants will also be identified from community settings who will act as participant identification centres (PICs). These PICs will conduct a search of the patient record database and suitable participants will be contacted either via letter, mailout or text to inform them about the study. Interested patients would contact the clinical trial site team directly for more information.

All delegated clinical trial site staff must be appropriately trained in order to carry out the study assessments and procedures, and this must be approved by the study coordination centre at Imperial College London who will provide the “green light” for participant recruitment once training has taken place and appropriate regulatory approvals have been received. The majority of training will be completed at the Site Initiation Visit (SIV). In particular, there will be training on data collection, responding to data queries and general information on obtaining high-quality research data.

3.5 LENGTH OF STUDY

The duration of the study is 22 months: 16 months recruitment and 6 months follow up (end of treatment phase is at 3 months; end of follow up is at 6 months). Recruitment started on 22 August 2023.

4. SELECTION AND WITHDRAWAL OF PARTICIPANTS

4.1 DIAGNOSTIC CRITERIA

4.1.1 DIABETES DIAGNOSTIC CRITERIA

A confirmed diagnosis of diabetes, either type 1 or type 2.

4.1.2 DIABETIC NEUROPATHY DIAGNOSTIC CRITERIA

For the purposes of the trial, a diagnosis of DN will be based on a validated screening questionnaire for DN using the Michigan Neuropathy Screening Instrument (MNSI) – a questionnaire score of ≥4, which is considered abnormal, and more sensitive and specific than the previously defined cut-off point of ≥7 (23,24)

4.1.3 NEUROPATHY SCREENING

Other causes of peripheral neuropathy will be excluded by taking a medical history.

The following blood tests will be collected and processed locally:

a. Folate
b. Vitamin B12
c. Thyroid function
d. HIV (optional)

Any abnormalities in blood test results will be recorded, patients will be excluded from the trial and receive appropriate written information. The patient's General Practitioner (GP) will be informed with the consent of the patient.

An additional HbA1c blood test will be collected at screening and Week 12, but this is not part of neuropathy screening.

4.2 INCLUSION CRITERIA

- Aged ≥18 (no upper limit)
- Diagnosis of type 1 or type 2 diabetes based on World Health Organisation (WHO) definition Diagnosis of diabetic neuropathy based on the validated screening questionnaire Michigan Neuropathy Screening Instrument score of ≥4
- Access to internet at home to use the Revitive App (study smartphones will be provided)

4.3 EXCLUSION CRITERIA

- Lacks capacity to provide informed consent
- Pregnant
- Implanted electronic, cardiac or defibrillator device
- Other cause of peripheral neuropathy
- Current foot ulceration
- Severe vascular disease requiring invasive intervention
- Being treated for, or have the symptoms of, an existing deep vein thrombosis (DVT)

- Regularly used a neuromuscular electrical stimulation (NMES) device within 1 year of randomisation

4.4 WITHDRAWAL CRITERIA

Once a participant has been enrolled, the clinical trial site will make every reasonable effort to keep in touch with the participant for the duration of the study (26 weeks). However, it is expected that approximately 10% of participants will be lost to follow up. Participants will be free to withdraw from any part of the study at any time without any effect on their usual medical care.

The local PI may withdraw participants from the study (after consultation with the CI) in order to protect their safety and/or if participants are unwilling to follow the protocol. All randomised participants who withdraw or are discontinued from the study will be considered off study device/on study and will be followed up until the study end (26 weeks), unless they specifically withdraw their consent to further follow up. The reason for their change of status and the study procedures and assessments they have withdrawn from will be recorded in the CRF/eCRF and medical records if offered by the participant.

5. PROCEDURES AND ASSESSMENTS

5.1 IDENTIFICATION AND PRESCREENING

Patients presenting with DN at the participating clinical trial sites will be considered for this study. They will be pre-screened by a member of the direct care team and invited to speak to a member of the clinical trial site team. In addition to clinical trial sites, potential participants will also be identified from community settings who will act as participant identification centres (PICs). These PICs will conduct a search of the patient record database and suitable participants will be contacted either via letter, mailout or text to inform them about the study. Interested patients would contact the clinical trial site team directly for more information. Advertisements for the trial will be placed in clinical trial sites, PICs and posted online and will include clinical trial site contact information.

Interested patients will be given a patient information sheet to read and will be given at least 24 hours before attending an appointment for written informed consent. A pseudonymised pre-screening log will identify all approached patients, with a minimum dataset of age, sex and reason for exclusion (if applicable).

5.2 VISIT 1 - RECRUITMENT AND CONSENT

Patients will be recruited from participating clinical trial sites in the UK. Consent to enter the study will be sought from each participant only after a full verbal explanation has been given, and a patient information sheet is offered at least 24 hours beforehand. Written informed consent will be obtained before the subject is enrolled in the study. Consent is a continuous process which will be assessed during the study.

If there are substantial changes to the protocol that require re-consent, the same process will be followed. An associated updated patient information sheet will be provided to participants prior to written informed re-consent.

5.3 EQUALITY, DIVERSITY AND INCLUSION

It is important that medical devices are trialled in diverse samples of participants. To address any potential bias in trial recruitment, the following will be in place:

- Data relating to equality and diversity (age, gender, disability, ethnicity, sexual orientation recruitment site) will be collected from study participants at the initial visit. Data will be monitored on a monthly basis by the Trial Management Group (TMG) to ensure that our research sample is representative of the diabetic population. Factors limiting equality and diversity in recruitment will be reviewed and addressed.
- Ms Liz Pigott, our patient representative from an ethnic minority background, can help ensure that our study remains inclusive and assist with building rapport with other members of the community.
- The inclusion criteria are broad so that certain demographics are not excluded.
- The study will be advertised online to improve accessibility for all potential participants.
- Translations of patient information sheets and consent forms (and other patient-facing documents) will be provided to improve accessibility to non-English speaking potential participants.

5.4 VISIT 1 – BASELINE

All study assessments will be performed by a blinded researcher. These assessments can be carried out over several days to reduce participant burden. After a participant has consented into the study, they will be formally assessed against the inclusion/exclusion criteria, and the following eligibility assessments will be completed:

- **Demographic information and vital signs** – Age, sex, ethnicity, date of birth, lifestyle, socioeconomic status, weight, height, blood pressure and pulse will be collected.
- **Clinical assessment** – Medical and drug history and other inclusion and exclusion criteria will be reviewed (i.e. whether the patient has other causes of peripheral neuropathy, severe vascular disease requiring invasive intervention, current foot ulceration prohibiting NMES device use, any implanted electronic, cardiac or defibrillator device prohibiting NMES device use, symptoms consistent with, or being treated for DVT, regularly used a NMES device within 1 year of randomisation). There are no prohibited concomitant medications for this trial.
- **Pregnancy test** – A pregnancy test will be performed for participants of childbearing potential. Participants must either be of non-childbearing potential OR be using adequate contraception for the duration of the study period and have a negative urine pregnancy test result. The urine from the point of care pregnancy test will be discarded immediately after the test is performed.
- **Blood tests** – Blood samples will be taken to exclude any other causes of DN (as mentioned in **4.1.3 NEUROPATHY SCREENING**). Blood tests will be collected and processed locally at sites.
- **Michigan Neuropathy Screening Instrument (MNSI)** – The MNSI is a validated screening system for distal symmetrical polyneuropathies (23,24). It comprises of a patient questionnaire and a separate clinical examination of the feet. Participants must be positively screened for DN, as demonstrated by a questionnaire score of ≥4 (24)

Once eligibility is confirmed, the following further assessments will take place:

- **Nerve conduction study (NCS) (central site only)** – The sural, common peroneal, tibial and superficial peroneal nerves will be bilaterally tested. All NCSs will be performed by a single, blinded researcher (a highly trained neurophysiologist) at the core lab at Imperial College Healthcare NHS Trust to reduce inter-operator variability. A separate **Nerve Conduction Study (NCS) Protocol** will outline how NCSs for this trial are conducted. If a NCS has been performed within 3 months of consent by the blinded researcher (a highly trained neurophysiologist) as part of standard of care, this NCS can be used instead, and it does not need to be repeated as part of the baseline visit.
- **Quantitative Sensory Testing (QST) (central site only)** – Somatosensory nerve fibre function will be assessed using the German Research Network on Neuropathic Pain (DFNS) QST protocol (29).

The battery of tests includes measures of cold and warm detection thresholds, paradoxical heat sensations, cold and heat pain thresholds, mechanical detection threshold, mechanical pain threshold, mechanical pain sensitivity, dynamic mechanical allodynia, temporal pain summation, vibration detection threshold and pressure pain threshold. Testing will take place on the worst affected limb.

- **Berg Balance Scale (BBS)** – Mobility and balance will be assessed using the validated measure (25).
- **Neuropathic Pain Symptom Inventory (NPSI)** – Neuropathic pain will be assessed using the validated measure (26).
- **Total Symptom Score (TSS)** – Symptoms (paraesthesia, pain, numbness, cramp and sleep disruption) will be assessed on a 10-point Numerical Rating Scale (NRS) and scores will be combined to give a TSS out of 50.
- **Monofilament test –** Protected sensation will be objectively assessed using a monofilament test. A 10g monofilament will be perpendicularly applied to five sites (1st, 3rd, and 5th metatarsal heads and plantar surface of the hallux and 3rd toe) of both feet for approximately two seconds each to cause the filament to bend. The participant will be asked if they felt the pressure applied or not at each site.
- **Patient diary** – Clinical trial site staff will provide a patient diary to participants to collect daily device usage for the 12-week treatment phase (i.e. adherence to treatment). Timed used and intensity level setting will be recorded. Although device usage will be collected via the Revitive App, a diary will also be provided to verify the Revitive App data collected.
- **Randomisation** – Once eligibility has been confirmed and additional baseline assessments completed, participants will be randomised to either the control group or intervention group by being allocated a study device code. They will also be assigned a pseudonymised study number unique to each individual enrolled on the trial using Sealed Envelope.
- **Device set-up and device sensory and suprathreshold** – Clinical trial site staff will assist in setting up the allocated study device for the participant and familiarise the participant with their device. Device set-up will include creating an account for the Revitive App and setting up the therapy plan on the participants study smartphone, which will be provided. The IFU will be provided for participants to take home for home device use.

  Participants will be familiarised with their allocated study device by being asked to place the soles of both feet onto the respective

footpads. Baseline device sensory and motor thresholds will be established by systematically increasing the stimulation intensity in increments of one whilst the participant provides verbal sensory feedback. The minimal intensity, at which the participant is able to clearly feel electrical stimulation, will be recorded as the sensory threshold; and that producing visible muscle twitches of the medial gastrocnemius will be the motor threshold. The stimulation intensity will be adjusted to produce visible but non-painful contraction of the lower limb musculature at twice the individual motor threshold or as much as the participant can tolerate as comfortable (suprathreshold) and this will be recorded. Participants will be instructed to use the device at the suprathreshold level (twice the individual motor threshold or as much as the participant can tolerate as comfortable). If participants do not perceive any sensation or muscle contractions, they should be encouraged to use their study device at the highest stimulation intensity (level 99), provided there are no other concerns with using the device at this level. Participants will complete their first treatment at the clinical trial site and will be advised to complete two 30-minute sessions a day, a minimum of five hours a week for 12 weeks at home. Usage will be recorded in a patient diary and Revitive App. Treatment session reminders will be issued via the Revitive App.

Device credibility and expectancy questionnaire – After completing their first treatment session, participants will be asked to complete a modified treatment credibility and expectancy questionnaire. This is a simple questionnaire to assess participants' treatment expectancy and rationale credibility as these factors may contribute to observed differences in outcomes (27).

5.5 VISIT 2 – WEEK 3, WEEK 6, WEEK 9 (TELEPHONE CALL)

At Week 3, Week 6 and Week 9, participants will be telephoned to see if they are tolerating the device. They will be asked to continue with treatment until the end of the treatment phase (12 weeks) and to increase the stimulation intensity of the device if they feel comfortable to do so, unless they are experiencing problems which require reducing the stimulation intensity level or stopping treatment, which will be based on clinical judgement of the local PI. If there are any concerns with safety, this will be escalated to the PI who will make a final decision on if unblinding is necessary (see **3.3 BLINDING PROCESS**).

At these follow up visits, participants will be told to inform the clinical trial site staff of any change in their medication or health. These AE (safety reporting) and concomitant medication checks are important as any changes may affect

their participation in the trial, although there are no prohibited concomitant medications for the trial.

At Week 6, the MNSI Part A questionnaire and TSS will also be completed over the telephone.

At Week 9, participants will be reminded to restart their therapy plan the following week on the Revitive App. A therapy plan will be set-up for participants at baseline by clinical trial site staff on the Revitive App, however, therapy plans in the Revitive App last for 10 weeks as standard. These will need to be restarted by participants at 10 weeks to complete the 3-month treatment phase. Re-starting therapy plans are also important to ensure participants continue to receive reminders to complete their treatment sessions.

5.6 VISIT 3 – WEEK 12 (END OF TREATMENT PHASE)

After 12 weeks of treatment, participants will be invited to return to hospital. This will mark the end of their treatment phase and they will return their allocated study device. Assessment and data collection will be collected as follows:

- Blood test (HbA1c only)
- Michigan Neuropathy Screening Instrument (MNSI)
- Nerve conduction study (NCS – bilateral testing of sural, common peroneal, tibial and superficial peroneal nerves) **(central site only)**
- Quantitative Sensory Testing (QST) **(central site only)**
- Berg Balance Scale (BBS)
- Neuropathic Pain Symptom Inventory (NPSI)
- Total Symptom Score (TSS)
- Monofilament test
- Device sensory threshold and suprathreshold
- Device experience questionnaire – A simple device use questionnaire will be taken to report ease of device use and suggest any developments
- Collection of patient diary
- AE (safety reporting) and concomitant medication check

5.7 VISIT 4 – WEEK 26 (FOLLOW UP)

At 26 weeks, participants will be invited to return to hospital. This will mark their final trial visit and completion of the study. Assessment and data collection will be collected as follows:

- Michigan Neuropathy Screening Instrument (MNSI)

- Nerve conduction study (bilateral testing of sural, common peroneal, tibial and superficial peroneal nerves) **(central site only)**
- Quantitative Sensory Testing (QST) **(central site only)**
- Mobility/Balance test (Berg Balance Scale)
- Neuropathic Pain Symptom Inventory (NPSI)
- Total Symptom Score (TSS)
- Monofilament test
- Device sensory threshold and suprathreshold
- AE (safety reporting) and concomitant medication check

5.8 INCIDENTAL FINDINGS

Incidental findings may potentially be identified during study assessments, such as blood and pregnancy tests. These will be reported to the GP with the consent of the patient.

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6. RECORD KEEPING AND DATA PROTECTION

6.1 SOURCE DATA

Participants in the study will be identified using a unique study number, which will be used to label all documentation. A list of patient details will be kept in a locked filing cabinet at the local clinical trial site. Data will be written directly into the CRF and then transcribed into the eCRF (REDCap). The Medical Dictionary for Regulatory Activities (MedDRA) dictionary will be used as the coding system for the study. Source documents include original documents related to the trial, medical treatment and history of the participant, and adequate source documentation will be maintained to allow reliable verification and validation of the trial data.

6.2 LANGUAGE

CRFs will be in English. All written material to be used by participants will use vocabulary that is clearly understood and be in the language appropriate for the study site.

6.3 DATABASE

The principal means of data collection and storage will be the eCRF, provided by the internet-based REDCap database system. Data will be entered into the eCRF system by clinical trial site staff and will be viewable through data entry access. The type of activity site staff may undertake on the database will be regulated by authorisations set up by the Trial Manager/Monitor. Where applicable, the option to select a value from a list of valid options will be

available. Valid rules and range checks, for example, will be set up on the database to ensure data integrity and queries will be generated by programmes designed to detect missing or erroneous data. The Trial Monitor will also be able to create data queries on missing or erroneous data identified through remote monitoring or source data verification. Clinical trial site staff will need to respond to these queries in a timely manner to ensure data integrity. Any data changes will also need to be updated on the source documentation and signed and dated by the clinical trial site staff to provide a paper trail. Regular reports will be sent to sites from the Trial Monitor detailing outstanding queries. All source data recorded in the CRF and data recorded in the eCRF will be signed by the local PI or delegate. All changes made following the electronic signing will have an electronic audit trail with a signature and date.

It is the policy of Imperial College London to retain all trial data for 10 years after a study has ended. All data, whether held electronically or manually, will be kept securely, backed up regularly (if electronic) and not disclosed unlawfully. The data custodian is Imperial College London. Actegy Limited will process the Revitive App data on behalf of Imperial College London and are therefore a data processor for this study.

6.4 MONITORING

The study will be monitored periodically to assess the progress of the study, verify adherence to the protocol, GCP guidelines and other national/international requirements and to review the completeness, accuracy and consistency of the data. Monitoring will be undertaken by the Trial Monitor and self-compliance checklists will be performed by site staff. Monitoring procedures and requirements will be documented in a **Monitoring Plan**, developed in accordance with the risk assessment and will follow a risk-based approach when determining the level of onsite and remote monitoring.

7. ASSESSMENT OF SAFETY

7.1 DEFINITIONS

7.1.1 INVESTIGATIONAL MEDICAL DEVICE

The medical device being assessed for safety or performance in a clinical investigation. This includes medical devices already on the market that are being evaluated for new intended uses, new populations, new materials or design changes.

The medical device being investigated for this trial is the Revitive Medic Coach. The device is suitable for healthy individuals or people with poor circulation, a sedentary lifestyle, limited mobility, following surgery or injury

and those with diabetes (including DN), osteoarthritis, peripheral arterial disease, chronic venous insufficiency and chronic obstructive pulmonary disease. The device is safe to use in patients and there are very few clinical risks associated with the use of NMES devices. There is no expected risk in patients with DN, if the exclusion criteria are adhered to.

Further details on the NMES device can be found in in the **Instructions for Use (IFU)** and **Investigator's Brochure (IB)**.

7.1.2 ADVERSE EVENT (AE)

An Adverse Event (AE) is any untoward medical occurrence, unintended disease or injury, or any untoward clinical signs (including an abnormal laboratory finding) in participants, users or other persons concerned with the medical device. These may, or may not be, considered related to the investigational device, device related procedure or comparator. If the AE is considered to have a reasonable causal relationship with the device, then it is considered to be an Adverse Device Effect (ADE).

7.1.3 ADVERSE DEVICE EFFECT (ADE)

An Adverse Event (AE) related to the use of an investigational medical device. This includes any AE resulting from insufficiencies or inadequacies in the instructions for use, the deployment, implantation or operation of the medical device or any malfunction. This also includes any AE that is a result of an error in use or intentional misuse of the medical device.

7.1.4 DEVICE DEFICIENCY

Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. Device deficiencies include malfunctions, misuse or use errors and inadequate labelling.

7.1.5 SERIOUS ADVERSE EVENT (SAE)

An Adverse Event (AE) that results in:

- Death.
- Life threatening illness or injury.
- Permanent impairment of a body structure or body function.
- Hospitalisation or prolongation of existing hospitalisation.
- Medical or surgical intervention to prevent life threatening illness, injury or impairment to a body structure or body function.
- Foetal distress, foetal death or congenital anomaly or birth defect.
- Is otherwise considered medically significant by the Investigator.

This includes potential SAEs which were avoided as result of action or intervention. A planned hospitalisation for a pre-existing condition, or a procedure required in the protocol, without a serious deterioration in health, is not considered an SAE.

NOTE: Device deficiencies that might have led to a SAE where a suitable action had not been taken or an intervention had not been made or if circumstances had been less fortunate are handled under the serious adverse event reporting system.

Such AEs should be reported as soon as possible.

Medical judgement should be exercised in deciding whether an adverse event is serious in other situations. Important adverse events that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

Severity: The term “severe” is often used to describe the intensity (severity) of a specific event. This is not the same as “serious”, which is based on patient/event outcome or action criteria.

7.1.6 SERIOUS ADVERSE DEVICE EFFECT (SADE)

An Adverse Device Effect (ADE) that results in:

- Death.
- Life threatening illness or injury.
- Hospitalisation, or prolongation of existing hospitalisation.
- Persistent or significant disability or incapacity.
- Foetal distress, foetal death or congenital anomaly or birth defect.
- Is otherwise considered medically significant by the Investigator.

But has previously been identified in the **Study Protocol** and/or **Investigator Brochure (IB)**.

Any hospitalisation planned prior to enrolment is not a SADE.

7.1.7 UNANTICIPATED SERIOUS ADVERSE DEVICE EFFECT (USADE)

Serious adverse device effect (SADE) which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

7.2 SAFETY RESPONSIBILITIES

There are a number of responsibilities when managing adverse events (AEs).

The CI has overall responsibility for the conduct of the study. The CI has co-ordinating responsibility for reporting adverse events (AEs) to the Medicines and Healthcare products Regulatory Agency (MHRA) and to the relevant Research Ethics Committee (REC).

The Principal Investigator (PI) has responsibility for the research at a local clinical trial site where the study involves specified procedures requiring site-specific assessment. There should be one PI for each research site. In the case of a single-site study, the CI and the PI should be the same person. The PI is responsible for informing the CI, or the coordinating research team, of all adverse events that occur at their site following the guidelines below.

7.2.1 INVESTIGATOR'S RESPONSIBILITIES

1. PI to report all SAEs within agreed timelines to the CI.
2. CI to report all SAEs within agreed timelines to Sponsor.
3. CI to report SAEs within agreed timelines to Sponsor, MHRA, REC and relevant NHS Trust Research and Development (R&D) Office. Only Unanticipated Serious Adverse Device Effects (USADEs) will be reported to the REC.
4. Provide the Sponsor with details of all AEs identified in the protocol as critical to the evaluation of safety within the agreed timeframes specified in the protocol.
5. Review SAE reports from Investigators and perform an evaluation with respect to seriousness, causality and expectedness.
6. Supply the Sponsor, MHRA, REC and relevant NHS Trust R&D with any supplementary information they request.

7.2.2 SPONSOR'S RESPONSIBILITIES

1. In collaboration with the Device Manufacturer, perform ongoing safety evaluation of the trial device and report any findings that may affect the health of subjects to the Device Manufacturer.
2. Promptly notify all Investigators, REC and MHRA, of any findings that may affect the health of subjects.
3. Keep detailed written reports of all AEs reported by PIs and performing an evaluation with respect to seriousness, causality and expectedness.
4. Report all relevant safety information and SAEs to the relevant REC and MHRA within the relevant timelines.
5. Break treatment codes before submitting expedited reports to MHRA and REC for specific subjects, even if the Investigator has not broken the code.

6. Submit the annual report to Sponsor and REC (if required).
7. Submit summary reports as required to the MHRA.

As this study is an Imperial College sponsored study, the above sponsor responsibilities will be delegated to the CI.

7.3 ASSESSMENT

7.3.1 CAUSALITY

Adverse reactions should be assessed for causality. The definitions below can be used.

Table 3: Definitions for causality assessment

Relationship	Description
Unrelated	There is no evidence of any causal relationship to the medical device
Unlikely	The relationship with the use of the investigational medical device seems not relevant and/or the event can be reasonably explained by another cause
Possible	The relationship with the use of the device is weak but cannot be ruled out completely
Probable	The relationship with the investigational medical device seems relevant and/or the event cannot be reasonably be explained by another cause
Causal Relationship	The serious event is associated with the investigational medical device beyond reasonable doubt

7.3.2 ASSESSMENT OF EXPECTEDNESS

Anticipated: The reaction is consistent with the effects of the device listed in the **Investigator Brochure (IB)** or **Study Protocol**.

Unanticipated: the reaction is not consistent with the effects of the device listed in the **Investigator Brochure (IB)** or **Study Protocol**.

7.4 REPORTING

Once the CI/PI has evaluated the AE in terms of seriousness, causality and expectedness, the following guidelines should be followed.

7.4.1 AEs/ADEs

For the purposes of the study, all AEs will be followed up until resolution or death of the participant. It is essential that all AEs that occur during the course of the study are appropriately reported in order to ensure the participants continuing safety. Of particular importance is the assessment of any event for causality and expectedness in relation to the device.

7.4.2 SAEs/SADEs

If the AE is assessed as serious, the PI **must** report the event to the CI **immediately or within 24 hours** of being made aware of the event. The initial report can be made via email but must be promptly followed with a detailed, written report. The PI must record the event with their assessment of seriousness, (along with causality, expectedness and severity) on a trial SAE form provided by the CI. The PI should ensure that follow up information is provided when available. **Where supporting documents are sent with this form, these must be pseudonymised.** Where the information available is incomplete at that time, as much information as can be ascertained should be sent to ensure timely reporting, with additional information provided as soon as it is known. Additional information received for an event (follow up or corrections to the original event data) needs to be detailed on a new SAE form.

In cases where the REDCap system is unavailable and the electronic SAE form cannot be completed, clinical trial sites will email the completed paper SAE form to the study coordination centre immediately or within 24 hours of being made aware of the event.

Study Coordination Centre Contact Details

Please send SAE forms via email to:
Sasha Smith
sasha.smith@imperial.ac.uk

or via post to:
Sasha Smith,
Section of Vascular Surgery
Room 16 4th Floor East Wing
Charing Cross Hospital
Fulham Palace Road
London W6 8RF
Tel: +44 (0)756 512 3056 (Mon to Fri 09.00 – 17.00)

7.4.3 SAEs REPORTING TO THE MHRA

The following must be reported to the MHRA by the delegated study coordination centre staff using the appropriate tabular reporting form.

a) Any SAE (whether initially considered to be device related or not)
b) Any Investigational Medical Device Deficiency that might have led to a SAE if,
    1. Suitable action had not been taken or
    2. Intervention had not been made or
    3. If circumstances had been less fortunate
c) New findings/updates in relation to already reported events

The CI should ensure that these are reported to the Imperial College Research Governance and Integrity Team (RGIT) within 24 hours. The tabular reporting form will give a cumulative overview of the reportable events per clinical investigation and will be updated and transmitted to the MHRA each time a new reportable event or a new finding to an already reported event is to be reported. More detailed information must be provided on request of the MHRA.

The study coordinating centre staff delegate will submit the completed MEDDEV 2/7/3 reporting spreadsheet to the MHRA's MORE portal quoting the MHRA's CI reference number. SAEs which indicate an imminent risk of death, serious injury or serious illness and require prompt remedial action for other patients, users or other persons or a new finding to it, must be reported to the MHRA by the CI **immediately** but not later than 2 calendar days following the date the Sponsor is made aware, using the summary tabulation form.

Any other reportable events should be reported **immediately** but not later than **7** calendar days following the date the Sponsor is made aware, using the same summary tabulation. The device manufacturer should also be informed within 24 hours of the SAE or device deficiency if indicated in the study's communication agreement.

The PI/CI must send all SAE reports to the Research Governance and Integrity Team, Imperial College AHSC immediately or within 24 hours after becoming aware of the event at the below address:

RGIT@imperial.ac.uk

Local research governance procedures at each site, e.g. NHS Trust, should also be followed.

7.4.4 USADEs

If an SAE is determined to be unanticipated (not previously described in the **Investigator Brochure (IB)** or **Study Protocol**) and related to the study device then it is considered an USADE. For USADEs, in addition to reporting to the MHRA as described in the sections above, the CI must also report the event to the REC in the UK and make sure the event is reported to Ethics Committees in participating countries as required. Reports should be made to the REC within **15 days** according to HRA website using the non-CTIMP SAE form. The Device Manufacturer and Investigators at all sites should be notified of the USADE.

Unblinding might have to be considered in the event of a USADE, although unblinding should be avoided where possible.

7.4.5 URGENT SAFETY MEASURES

The CI and PIs have the authority to deviate from the protocol if doing so relates to the immediate safety of a participant, where continuing to follow protocol would put that participant at risk. This is classed as an urgent safety measure and must be reported to the RGIT, MHRA and REC within three calendar days of the occurrence. This may be reported verbally in the first instance but must be supported by a written report as soon as information is available.

7.4.6 PREGNANCY

Where relevant, any pregnancy occurring during the clinical study and the outcome of the pregnancy should be recorded on a Pregnancy Notification Form. Patients will be asked to consent to be followed up for congenital abnormality or birth defect. Pregnancy is considered an SAE, the patient will be asked to stop using the device, followed up according to the protocol and the results analysed as per intention to treat.

7.5 ANNUAL PROGRESS REPORTS

An annual progress report should be submitted to the REC which gave the favourable opinion 12 months after the date of the favourable opinion letter. The annual progress report should be emailed to REC within 30 days of this reporting period. The requirement to submit annual progress reports to the REC ceased on 01 August 2024.

7.6 TREND ANALYSES

The CI in conjunction with the manufacturer should undertake trend analysis regarding the safety of the device.

8. STATISTICAL ANALYSES

8.1 SAMPLE SIZE CONSIDERATIONS

The target sample size is 64 participants (32 participants per group), which includes an expected 10% loss to follow up rate at 6 months. Therefore, the final number of participants with primary outcome measure data is expected to be 57.

As the previous research in this area has been limited, and the treatment effect of NMES on DN is unclear, a sample size could not be determined using a power calculation. A previous proof-of-concept study found a mean reduction of 1.75 points in the total score of the MNSI Part A questionnaire after 10 weeks of NMES therapy (22). For the defined objectives, the chosen target is realistic to achieve in this clinical setting and provide sufficient pilot data to assess the potential efficacy signal, feasibility and safety of a NMES device. This study will serve as the foundation for future powered RCTs investigating NMES in DN.

Further details on sample size and minimal clinically important difference considerations will be included in the **Statistical Analysis Plan (SAP)**, authored by members of the statistical support team and agreed by the Trial Management Group (TMG). The **SAP** will be finalised prior to database lock.

8.2 PLANNED DATA ANALYSES

The primary and safety analyses will be performed based on the intention-to-treat (ITT) principle. This is defined as all participants confirmed as eligible at screening and randomised, regardless of treatment adherence. The follow up phase for these participants will be 26 weeks in total (with primary outcome measured at 12 weeks). These analyses will exclude all those who specifically asked to be withdrawn and requested for their data not to be used for the trial.

There are no planned interim analyses. Sensitivity analyses will be conducted to assess the robustness of the conclusions. Non-compliance will be assessed through per protocol (PP) analyses, including participants with no protocol violations or major deviations. The two populations of interest: the intention to treat (ITT) population and the per-protocol (PP) population for potential clinical efficacy will be determined prior to database lock and release of the randomisation.

The impact of missing data will also be investigated. Prior to data analysis, the level and pattern of missing data will be established by creating appropriate tables. There will be a summary table with reasons for missing data, in particular primary outcome data measured at 12 weeks. For the main

analysis, missing data will be assumed to be missing at random (MAR) and multiple imputation will be used. To assess the impact of any bias due to missing data, a sensitivity analysis on the primary endpoint will be performed, where missing data will assumed to be missing not at random (MNAR). This may include copy-reference imputation, where the missing data are assumed to have a profile that is the same as that of the control group.

Subgroup analyses will investigate the effect of the intervention among subgroups, such as those with different severities of DN and those with different types of diabetes.

Quantitative data will be analysed using SAS statistical software. Following tests for normality, standard descriptive parameters for each study outcome will be calculated, either for parametric (e.g. mean, standard deviation) and non-parametric (e.g. medium, interquartile range) data. This will be calculated for the actual value at each timepoint and the change from baseline. Data will also be presented graphically.

Further details on the planned data analyses, including the primary outcome measure, feasibility outcome measures, safety outcome measures and secondary outcome measures, will be included in the **SAP**, authored by members of the statistical support team and agreed by the Trial Management Group (TMG). The **SAP** will be finalised prior to database lock.

8.2.1 PRIMARY OUTCOME MEASURE ANALYSIS

The primary outcome measure is the MNSI Part A questionnaire total score, which measures neuropathy symptoms using at 12 weeks. The difference in change in the MNSI Part A questionnaire total score, between the two treatment groups at 6 weeks, 12 weeks and 26 weeks will be analysed using Analysis of Covariance (ANCOVA) models. The primary timepoint of interest is at 12 weeks, but neuropathy symptoms at 6 weeks and 26 weeks will also be evaluated. Each model will include a term for treatment and baseline MNSI Part A questionnaire total score as a covariate. The ANCOVA will be applied to each of the multiply imputed datasets and then combined using Rubin's method. If the assumptions underlying the ANCOVA are violated, alternative non-parametric methods, such as a rank ANCOVA will be considered. A p value of ≤ 0.05 is to be considered significant. Full details of the multiple imputation process will be provided in the **SAP**.

8.2.2 FEASIBILITY OUTCOME MEASURES ANALYSIS

Feasibility outcome measures include recruitment rate measured using screening and randomisation logs, participant retention rate measured using randomisation and withdrawal logs and treatment adherence rate measured using Revitive App and a patient diary. The data for these parameters will be summarised descriptively. Since this is the first time the Revitive App is being used to collect treatment adherence data in this patient population, the data collected from the Revitive App and patient diary will be compared to see if there is agreement between these two data collection methods.

8.2.3 SAFETY OUTCOME MEASURES ANALYSIS

All safety variables will be summarised by treatment in the form of frequency tables for categorical variables or descriptive statistics for continuous variables. The MedDRA dictionary will be used as the coding system for the study. An AE will be considered treatment emergent if it started after the first use of the device (NMES or sham device). Adverse events will be categorised by MedDRA System Organ Class and Preferred Term. Treatment emergent AEs will also be summarised (incidence and frequency) by severity and relationship to treatment.

8.2.4 SECONDARY OUTCOME MEASURES ANALYSIS

Secondary outcomes include, but are not limited to, sural, superficial peroneal, common peroneal and tibial nerve conductivity, somatosensory nerve fibre function, mobility and balance, quality of life, neuropathy signs and symptoms, protective sensation, neuropathic pain and device sensation. Secondary outcome measures will be analysed using appropriate statistical models with appropriate adjustments to investigate the difference in outcomes between the two treatment groups at baseline, 12 weeks and 26 weeks. Other outcomes such as device experience (patient questionnaire recorded at Week 12) will be summarised descriptively.

Intergroup comparisons of categorical variables will be analysed using chi-squared test.

9. REGULATORY ISSUES

9.1 ETHICS APPROVAL

The Study Coordination Centre has obtained approval from the North East - Newcastle & North Tyneside 2 Research Ethics Committee (REC) and Health Research Authority (HRA). The study must also receive confirmation of capacity and capability (or applicable approval) from each participating NHS site before accepting participants into the study or any research activity is

carried out. The study will be conducted in accordance with the study protocol and GCP guidelines.

9.2 AMENDMENTS

Any changes to the protocol which will impact the conduct of the study, potential benefit to the patient or may affect patient safety, including changes of study objectives, study design, patient population, sample sizes, study procedures or significant administrative aspects will require a formal amendment to the protocol, which will need to be submitted and approved by regulatory authorities.

Minor administration changes and clarifications that have no effect on the way the study is conducted will be submitted to the Sponsor and may require further regulatory approvals.

9.3 CONSENT

Consent to enter the study will be sought from each participant only after a full explanation has been given, a patient information leaflet is offered, and adequate time allowed (at least 24 hours) for consideration. Signed participant consent will be obtained. The right of the participant to refuse to participate without giving reasons will be respected. After the participant has entered the trial, the clinician remains free to give alternative treatment to that specified in the protocol at any stage if he/she feels it is in the participant's best interest, but the reasons for doing so should be recorded. In these cases, the participants remain within the study for the purposes of follow up and data analysis. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment. A participant's GP will be notified via letter of study inclusion if the participant consents to this communication.

9.4 CONFIDENTIALITY

The investigator must ensure that the subject's confidentiality is maintained on the CRF/eCRF or other documents submitted to the Sponsor, or on anonymised safety information provided to the device manufacturer, subjects will be identified by a unique study number only. Documents that are held by the study coordination centre or clinical trial sites (e.g., signed informed consent form) should be kept in a lockable office in a strictly confidential file by the researchers.

The local PI shall permit direct access to subjects' records and source documents for the purposes of monitoring, auditing or inspection by the

Sponsor, authorised representatives of the Sponsor, NHS and regulatory authorities. The site will preserve the confidentiality of participants taking part in the study and is registered under the Data Protection Act.

9.5 ACCESS TO DATA

This study has planned data sharing activities with Actegy Limited. Anonymised data will be shared with the device manufacturer and study funder Actegy Limited in accordance with a data sharing agreement at the end of the trial (after last patient last visit).
Other data sharing requests may be made outside the sponsor organisation and will be made under a data sharing agreement that provides the following:

1. A commitment to using the data only for research purposes and not to identify any individual participant;
2. A commitment to securing the data using appropriate computer technology;
3. A commitment to destroying or returning the data after analyses are completed.

All data sharing requests will be assessed, accepted and approved by the CI. A record of all access to data will be maintained by the Trial Manager.

9.6 INDEMNITY

Imperial College London holds negligent harm and non-negligent harm insurance policies which apply to this trial.

9.7 SPONSOR

Imperial College London will act as the main Sponsor for this study. Delegated responsibilities will be assigned to the centres taking part in this study.

9.8 STUDY MANAGEMENT

A Trial Management Group (TMG) will be convened including the Chief Investigator, co-investigators, statistician, trial manager, trial monitor and key collaborators. The TMG will be responsible for day-to-day conduct of the trial and operational issues. Details of membership, responsibilities and frequency of meetings will be defined in separate **Terms of Reference.**

Any disruptions to the trial due to COVID-19, or similar circumstances, will be discussed with the TMG. Remote follow up visits (with physical assessments performed later) may be suggested if it is not appropriate for participants to attend on-site.

Due to the minimal risks of NMES interventions applied at the lower limb, a Data Monitoring Committee (DMC) will not be convened for this study.

9.9 PATIENT AND PUBLIC INVOLVEMENT (PPI)

Patients and the public have been involved in the design of the trial and will continue to be involved in further trial stages. The following PPI activities have taken place / are planned:

- Design of the research: Patients have identified this research as a priority. The research team have spoken with patients suffering from DN, who have told them that current management strategies for DN are inadequate and that new treatments must be researched. Patient representatives have reviewed the patient-facing materials to check they are easy to understand and have provided patient perspectives on the inclusion of a sham device and masking this from participants. Furthermore, interviews have taken place with patients suffering from DN to identify the barriers and facilitators of NMES as a potential treatment, which has informed the design of the study. In sum, barriers were perception of safety and potential lack of sensation. Facilitators included device usability, independence, health motivators and following a routine. Based on these findings, we have added a period of device familiarisation into the study protocol and included regular contact and engagement with participants during their treatment period. This aims to promote independence, education, establishing motivations early and promoting these behaviours throughout.
- Management of the research: Two patient representatives have expressed interest in remaining active in the study as advisors at various points throughout the study.
- Dissemination of results: Patient representatives will also be invited to provide perspectives on the dissemination of the study findings including how best to communicate these to study participants and other patient groups.

9.10 FUNDING

This trial is funded by Actegy Limited. The study coordination centre will provide regular study progress reports to Actegy Limited.

9.11 AUDITS AND INSPECTIONS

The study will be subject to inspection and audit by Imperial College London under their remit as Sponsor, the study coordination centre and other regulatory authorities to ensure adherence to GCP.

9.12 CONFLICTS OF INTEREST

Professor Alun Davies and Miss Sasha Smith are supported by research grants from Actegy Limited, the funder and device manufacturer for this study.

9.13 PUBLICATION POLICY

All publications and presentations relating to the study will be authorised by the CI. Terms of authorship will be agreed with all contributors. Authorship of parallel studies initiated will be according to the individuals involved in the project but must acknowledge the contribution of the study. The study will be published in a peer reviewed journal, and available from the researchers on request. A lay summary of the results will be provided to participants.

10. APPENDICES

10.1 VISIT SCHEDULE

PROCEDURES AND ASSESSMENTS	PRESCREENING / IDENTIFICATION	VISIT 1 BASELINE[1]	VISIT 2 WEEK 3	VISIT 3 WEEK 6	VISIT 4 WEEK 9	VISIT 5 WEEK 12	VISIT 6 WEEK 26
Pre-screening	X						
Informed Consent		X					
Demographics		X					
Vital signs		X					
Clinical assessment (Medical and drug history etc.)		X					
Pregnancy test		X					
Blood tests		X				X	
Nerve conduction study (NCS)[2]		X				X	X
Quantitative Sensory Testing (QST)[2]		X				X	X
Michigan Neuropathy Screening Instrument (MNSI)		X		X		X	X
Berg Balance Scale (BBS)		X				X	X
Neuropathic Pain Symptom Inventory (NPSI)		X				X	X
Total Symptom Score (TSS)		X		X		X	X
Monofilament test		X				X	X
Issue patient diary		X					
Randomisation		X					
Device set-up		X					

Device sensory and suprathreshold		X				X	X
Device credibility and expectancy questionnaire		X					
Collect patient diary						X	
Device experience questionnaire						X	
AE (safety reporting) and concomitant medications check			X	X	X	X	X
Device toleration			X	X	X	X	X

1. **Baseline (Visit 2):** Allowed be performed across multiple days.

2. Performed at Imperial College Healthcare NHS Trust (central site) only.

10.2 SIGNATURE PAGE (CHIEF INVESTIGATOR)

The signature of the below constitutes agreement of this protocol by the signatory and provides the necessary assurance that this study will be conducted at his/her investigational site according to all stipulations of the protocol including all statements regarding confidentiality.

Study Title:	Neuromuscular Electrical Stimulation For The Treatment Of Diabetic Neuropathy: A Multi-centre, Double-blind, Pilot, Randomised, Sham-controlled Trial (NMES-DN)
Protocol Version:	12.0
Address of Institution:	
Signed:	
Print Name and Title:	
Date:	

10.3 SIGNATURE PAGE (SPONSOR)

The signature of the below constitutes agreement of this protocol by the signatory and provides the necessary assurance that this study will be conducted at his/her investigational site according to all stipulations of the protocol including all statements regarding confidentiality.

Study Title:	Neuromuscular Electrical Stimulation For The Treatment Of Diabetic Neuropathy: A Multi-centre, Double-blind, Pilot, Randomised, Sham-controlled Trial (NMES-DN)
Protocol Version:	12.0
Address of Institution:	
Signed:	
Print Name and Title:	
Date:	

10.4 SIGNATURE PAGE (PRINCPAL INVESTIGATOR)

The signature of the below constitutes agreement of this protocol by the signatory and provides the necessary assurance that this study will be conducted at his/her investigational site according to all stipulations of the protocol including all statements regarding confidentiality.

Study Title:	Neuromuscular Electrical Stimulation For The Treatment Of Diabetic Neuropathy: A Multi-centre, Double-blind, Pilot, Randomised, Sham-controlled Trial (NMES-DN)
Protocol Version:	12.0
Address of Institution:	
Signed:	
Print Name and Title:	
Date:	

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