# Investigating whether a device that provides neuromuscular electrical stimulation can improve nerve function in the legs of people with diabetic neuropathy

Submission date	<b>Recruitment status</b> No longer recruiting	[X] Prospectively registered		
21/06/2023		[X] Protocol		
Registration date	Overall study status Completed	Statistical analysis plan		
30/06/2023		☐ Results		
Last Edited	Condition category	Individual participant data		
02/04/2025	Nutritional, Metabolic, Endocrine	[X] Record updated in last year		

# Plain English summary of protocol

Background and study aims

Around half of people with diabetes experience nerve damage called diabetic neuropathy. The nerve damage commonly occurs in the feet and legs and can lead to symptoms such as numbness, pain and hypersensitivity. The cause of diabetic neuropathy is thought to be due to nerves not functioning properly and poor circulation in the blood vessels that supply the nerves. A new device has become available to improve nerve function in the legs by directly stimulating nerves and increasing blood flow in the legs. This study aims to look at its effect on people with damaged nerves in the legs.

#### Who can participate?

Adults aged over 18 years old with diabetes-related nerve problems in their legs

#### What does the study involve?

Participants will receive a study device in addition to the standard of care for 12 weeks. Participants will be asked to use their 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 comfortably). If participants do not perceive any sensation or muscle contractions, they will 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. Participants will receive a telephone call at 3 weeks, 6 weeks and 9 weeks and will be invited back to the clinic for tests at 12 weeks and 26 weeks.

#### What are the possible benefits and risks of participating?

We know from previous studies that Revitive devices increase blood flow in healthy people. We expect it to do the same for patients with diabetic neuropathy, so there will be a direct benefit to study participants. The device has been through the national testing process and is safe to use for healthy individuals to improve circulation. This study aims to look at its effect on people

with diabetic neuropathy as the device has not been tested extensively in these individuals. However, additional risks for this patient group are not anticipated.

Where is the study run from? Imperial College London (UK)

When is the study starting and how long is it expected to run for? October 2016 to June 2025

Who is funding the study?
Actegy Ltd, the neuromuscular electrical stimulation device manufacturer (UK)

Who is the main contact?
Miss Sasha Smith (Imperial College London), sasha.smith@imperial.ac.uk

# **Contact information**

# Type(s)

**Public** 

#### Contact name

Miss Sasha Smith

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Scientific

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#### Type(s)

Principal Investigator

#### Contact name

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# Additional identifiers

# **EudraCT/CTIS** number

Nil known

#### **IRAS** number

237312

## ClinicalTrials.gov number

NCT03767478

# Secondary identifying numbers

18HH4610, IRAS 237312

# Study information

#### Scientific Title

NeuroMuscular Electrical Stimulation for the treatment of Diabetic Neuropathy: A multi-centre, double-blind, pilot, randomised, sham-controlled trial (NMES-DN)

#### Acronym

**NMES-DN** 

# Study objectives

Current study hypothesis as of 20/12/2024:

Primary outcome null hypothesis (H0): There is no statistically significant difference in change in neuropathy symptoms measured using the Michigan Neuropathy Screening Instrument (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 (H1): There is a statistically significant difference in

change in neuropathy symptoms measured using the Michigan Neuropathy Screening Instrument (MNSI) Part A questionnaire total score, between the control and intervention groups from baseline to the end of the treatment phase (12 weeks).

#### Previous study hypothesis:

Primary outcome measure hypotheses

Primary outcome null hypothesis (H0): There is no statistically significant difference in change in sural nerve conductivity, specifically the conduction velocity (m/s) or the sensory nerve action potential (SNAP) amplitude ( $\mu$ V), between the control and intervention groups from baseline to the end of the treatment phase (6 months).

Primary outcome alternative hypothesis (H1): There is a statistically significant difference in change in sural nerve conductivity, specifically the conduction velocity (m/s) or the sensory nerve action potential (SNAP) amplitude ( $\mu$ V), between the control and intervention groups from baseline to the end of the treatment phase (6 months).

# Ethics approval required

Ethics approval required

#### Ethics approval(s)

Approved 23/10/2018, North East - Newcastle & North Tyneside 2 Research Ethics Committee (NHSBT Newcastle Blood Donor Centre, Holland Drive, Newcastle upon Tyne, NE2 4NQ, United Kingdom; +44 (0)2071048082; newcastlenorthtyneside2.rec@hra.nhs.uk), ref: 18/NE/0281

## Study design

Multi-centre double-blind pilot randomized sham-controlled trial

# Primary study design

Interventional

# Secondary study design

Randomised controlled trial

# Study setting(s)

Hospital, Telephone

# Study type(s)

Treatment, Safety, Efficacy

# Participant information sheet

Not available in web format, please use the contact details to request a patient information sheet

# Health condition(s) or problem(s) studied

Patients with diabetic neuropathy

#### **Interventions**

Current interventions as of 20/12/2024:

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.

For the purpose of the trial, all participants will be asked to use their study device for two 30-minute sessions per day, a minimum of five hours per week for 3 months 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 will 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.

#### Previous interventions:

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.

For the purpose of the trial, all participants will be asked to use their study device for two 30-minute sessions per day, a minimum of five hours per week for 6 months 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 will 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.

#### Intervention Type

Device

# Pharmaceutical study type(s)

Not Applicable

#### Phase

Not Applicable

#### Drug/device/biological/vaccine name(s)

Revitive Medic Coach neuromuscular electrical stimulation

#### Primary outcome measure

Current primary outcome measure as of 20/12/2024:

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

#### Previous primary outcome measure:

Sural nerve conductivity measured using a nerve conduction study at month 6 (Primary), and month 9. This includes conduction velocity (m/s), calculated using distance and latency (ms), and sensory nerve action potential (SNAP) amplitude (µV).

Current secondary outcome measures as of 20/12/2024:

Feasibility outcome measures:

- 1. Recruitment rate measured using screening and randomisation logs at pre-screening / identification, recruitment and consent, and baseline
- 2. Participant retention rate measured using randomisation and withdrawal logs at recruitment and consent, baseline, week 12, week 26
- 3. Adherence to treatment measured using Revitive App and a patient diary at week 12

#### Safety outcome measures:

- 1. Adverse Events (AEs) collected and reported via AE form at baseline, week 3, week 6, week 9, week 12, week 26 (and any communication in between)
- 2. Adverse Device Effects (ADEs) collected and reported via AE form at baseline, week 3, week 6, week 9, week 12, week 26 (and any communication in between)
- 3. Serious Adverse Events (SAEs) collected and reported via SAE form at baseline, week 3, week 6, week 9, week 12, week 26 (and any communication in between)
- 4. Serious Adverse Device Effects (SADEs) collected and reported via SAE form at baseline, week
- 3, week 6, week 9, week 12, week 26 (and any communication in between)

- 1. Sural nerve conductivity (central site only) measured using a nerve conduction study, includes conduction velocity (m/s), calculated using distance and latency (ms), and sensory nerve action potential (SNAP) amplitude ( $\mu$ V) at week 12 and week 26
- 2. Superficial peroneal nerve conductivity (central site only) measured using a nerve conduction study, includes conduction velocity (m/s), calculated using distance and latency (ms), and sensory nerve action potential (SNAP) amplitude ( $\mu$ V) at week 12 and week 26
- 3. Common peroneal nerve conductivity (central site only) measured using a nerve conduction study, 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) at week 12 and week 26
- 4. Tibial nerve conductivity (central site only) measured using a nerve conduction study, including conduction velocity (m/s), calculated using distance and distal latency (ms), Compound Muscle Action Potential (CMAP) amplitude (mV) and minimum F wave latency (ms) at week 12 and week 26
- 5. Somatosensory nerve fibre function (central site only) measured using Quantitative Sensory Testing (QST) at week 12 and week 26
- 6. Blood glucose measured using HbA1c at week 12
- 7. Mobility and balance measured using a validated Berg Balance Scale (BBS) at week 12 and week 26
- 8. Neuropathy signs measured using a validated screening questionnaire, Michigan Neuropathy Screening Instrument (MNSI) Part B Examination at week 12 and week 26
- 9. Symptoms measured using Total Symptom Score at week 6, week 12 and week 26
- 10. Protected sensation measured using monofilament test at week 12 and week 26
- 11. Neuropathic pain measured using Neuropathic Pain Symptom Inventory (NPSI) at week 12 and week 26
- 12. Device sensation measured using device sensory threshold and suprathreshold at week 12 and week 26
- 13. Device experience measured using a device experience questionnaire at week 12
- 14. Device credibility and expectancy measured using modified credibility and expectancy questionnaire at baseline

#### Previous secondary outcome measures as of 13/07/2023:

#### Feasibility outcome measures

- 1. Recruitment rate measured using screening and randomisation logs at pre-screening / identification, recruitment and consent, and baseline
- 2. Participant retention rate measured using randomisation and withdrawal logs at recruitment and consent, baseline, month 6
- 3. Adherence to treatment measured using Revitive App and a patient diary at month 6

#### Safety outcome measures

- 1. Adverse Events (AEs) collected and reported via AE form at baseline, week 2, month 6, month 9 (and any communication in between)
- 2. Adverse Device Effects (ADEs) collected and reported via AE form at baseline, week 2, month 6, month 9 (and any communication in between)
- 3. Serious Adverse Events (SAEs) collected and reported via SAE form at baseline, week 2, month 6, month 9 (and any communication in between)
- 4. Serious Adverse Device Effects (SADEs) collected and reported via SAE form at baseline, week 2, month 6, month 9 (and any communication in between)

- 1. Superficial peroneal nerve conductivity measured using a nerve conduction study, includes conduction velocity (m/s), calculated using distance and latency (ms), and sensory nerve action potential (SNAP) amplitude ( $\mu$ V) at months 6 and 9
- 2. Common peroneal nerve conductivity measured using a nerve conduction study, 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) at months 6 and 9
- 3. Tibial nerve conductivity measured using a nerve conduction study, including conduction velocity (m/s), calculated using distance and distal latency (ms), Compound Muscle Action Potential (CMAP) amplitude (mV) and minimum F wave latency (ms) at months 6 and 9
- 4. Somatosensory nerve fibre function measured using Quantitative Sensory Testing (QST) at months 6 and 9
- 5. Mobility and balance measured using validated Berg Balance Scale (BBS) at months 6 and 9
- 6. Quality of life measured using a validated EQ-5D-5L questionnaire at months 6 and 9
- 7. Illness perceptions measured using validated Brief Illness Perception Questionnaire (Brief IPQ) at months 6 and 9
- 8. Neuropathy signs and symptoms measured using a validated screening questionnaire, Michigan Neuropathy Screening Instrument (MNSI) at months 6 and 9
- 9. Neuropathy symptoms measured using validated Self-administered Neuropathy Total Symptom Score (NTSS-6-SA) at months 6 and 9
- 10. Protected sensation measured using monofilament test at months 6 and 9
- 11. Pain neuropathic pain measuring using Neuropathic Pain Symptom Inventory (NPSI) at months 6 and 9, and daily pain measured using an 11-point Numerical Rating Scale (NRS) collected via text message daily for the treatment phase (6 months)
- 12. Sleep interference daily sleep interference measured using Daily Sleep Interference Scale (DSIS) collected via text message daily for the treatment phase (6 months)
- 13. Peripheral arterial perfusion measured using Ankle Brachial Pressure Index (ABPI) at baseline
- 14. Device sensation measured using device sensory threshold and suprathreshold at months 6 and 9
- 15. Device experience measured using a device experience questionnaire at month 6
- 16. Device credibility and expectancy measured using modified credibility and expectancy questionnaire at baseline

Previous secondary outcome measures:

#### Feasibility outcome measures

- 1. Recruitment rate measured using screening and randomisation logs at pre-screening / identification, recruitment and consent, and baseline
- 2. Participant retention rate measured using randomisation and withdrawal logs at recruitment and consent, baseline, month 6
- 3. Adherence to treatment measured using Revitive App and a patient diary at month 6

#### Safety outcome measures

- 1. Adverse Events (AEs) collected and reported via AE form at baseline, week 2, month 6, month 9 (and any communication in between)
- 2. Adverse Device Effects (ADEs) collected and reported via AE form at baseline, week 2, month 6, month 9 (and any communication in between)
- 3. Serious Adverse Events (SAEs) collected and reported via SAE form at baseline, week 2, month 6, month 9 (and any communication in between)
- 4. Serious Adverse Device Effects (SADEs) collected and reported via SAE form at baseline, week 2, month 6, month 9 (and any communication in between)

- 1. Superficial peroneal nerve conductivity measured using a nerve conduction study, includes conduction velocity (m/s), calculated using distance and latency (ms), and sensory nerve action potential (SNAP) amplitude ( $\mu$ V) at months 6 and 9
- 2. Common peroneal nerve conductivity measured using a nerve conduction study, 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) at months 6 and 9
- 3. Tibial nerve conductivity measured using a nerve conduction study, including conduction velocity (m/s), calculated using distance and distal latency (ms), Compound Muscle Action Potential (CMAP) amplitude (mV) and minimum F wave latency (ms) at months 6 and 9
- 4. Somatosensory nerve fibre function measured using Quantitative Sensory Testing (QST) at months 6 and 9
- 5. Mobility and balance measured using validated Berg Balance Scale (BBS) at months 6 and 9
- 6. Quality of life measured using a validated EQ-5D-5L questionnaire at months 6 and 9
- 7. Illness perceptions measured using validated Brief Illness Perception Questionnaire (Brief IPQ) at months 6 and 9
- 8. Neuropathy signs and symptoms measured using a validated screening questionnaire, Michigan Neuropathy Screening Instrument (MNSI) at months 6 and 9
- 9. Neuropathy symptoms measured using validated Self-administered Neuropathy Total Symptom Score (NTSS-6-SA) at months 6 and 9
- 10. Protected sensation measured using monofilament test at months 6 and 9
- 11. Pain neuropathic pain measuring using Neuropathic Pain Symptom Inventory (NPSI) at months 6 and 9, and daily pain measured using an 11-point Numerical Rating Scale (NRS) collected via text message daily for the treatment phase (6 months)
- 12. Sleep interference daily sleep interference measured using Daily Sleep Interference Scale (DSIS) collected via text message daily for the treatment phase (6 months)
- 13. Peripheral arterial perfusion measured using Ankle Brachial Pressure Index (ABPI) at months 6 and 9
- 14. Device sensation measured using device sensory threshold and suprathreshold at months 6

#### and 9

15. Device experience – measured using a device experience questionnaire at month 6

16. Device credibility and expectancy – measured using modified credibility and expectancy questionnaire at baseline

# Overall study start date

01/10/2016

#### Completion date

30/06/2025

# **Eligibility**

## Key inclusion criteria

Current inclusion criteria as of 20/12/2024:

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

#### Previous inclusion criteria:

- 1. Aged ≥18 years (no upper limit)
- 2. Diagnosis of type 1 or type 2 diabetes based on World Health Organisation (WHO) definition
- 3. Diagnosis of diabetic neuropathy based on:
- 3.1. Symptoms of diabetic neuropathy
- 3.2. Validated screening questionnaire Michigan Neuropathy Screening Instrument score of ≥4
- 3.3. Nerve conduction study of at least one lower limb must have a sural sensory nerve action potential (SNAP) amplitude of  $<6 \,\mu\text{V}$  or absent
- 4. Access to the internet at home to use the Revitive App (study smartphones will be provided)
- 5. Personal mobile phone to receive text messages

#### Participant type(s)

Patient

#### Age group

Adult

#### Lower age limit

18 Years

#### Sex

Both

#### Target number of participants

64

#### Total final enrolment

65

#### Key exclusion criteria

Current exclusion criteria as of 20/12/2024:

- 1. Lacks the capacity to provide informed consent
- 2. Pregnant
- 3. Implanted electronic, cardiac or defibrillator device
- 4. Other causes of peripheral neuropathy
- 5. Current foot ulceration
- 6. Severe vascular disease requiring invasive intervention
- 7. Being treated for, or having the symptoms of, an existing deep vein thrombosis (DVT)
- 8. Regularly used a neuromuscular electrical stimulation (NMES) device within 1 year of randomisation

#### Previous exclusion criteria:

- 1. Lacks the capacity to provide informed consent
- 2. Pregnant
- 3. Implanted electronic, cardiac or defibrillator device
- 4. Other causes of peripheral neuropathy (e.g. excessive drinking, low levels of vitamin B12 or other vitamins, syphilis, HIV, underactive thyroid gland)
- 5. Current foot ulceration
- 6. Severe vascular disease requiring invasive intervention
- 7. Being treated for, or having the symptoms of, an existing deep vein thrombosis (DVT)
- 8. Used a neuromuscular electrical stimulation (NMES) device within 1 year of randomisation

#### Date of first enrolment

23/08/2023

## Date of final enrolment

31/12/2024

# Locations

#### Countries of recruitment

England

United Kingdom

# Study participating centre Imperial College Healthcare NHS Trust

Charing Cross Hospital Fulham Palace Road London United Kingdom W6 8RF

Study participating centre
Mid and South Essex NHS Foundation Trust
Basildon University Hospital

Nethermayne Basildon Essex United Kingdom SS16 5NL

# Sponsor information

# Organisation

Imperial College London

#### Sponsor details

Research Governance and Integrity Team (RGIT)
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rgit@imperial.ac.uk

#### Sponsor type

University/education

#### Website

http://www.imperial.ac.uk/

#### **ROR**

https://ror.org/041kmwe10

# Funder(s)

#### Funder type

Industry

#### **Funder Name**

Actegy Ltd

# **Results and Publications**

# Publication and dissemination plan

- 1. Publication in a peer-reviewed journal
- 2. Presentation of results at national and international conferences
- 2. Summaries of results made available to local investigators for dissemination within their clinical areas (where appropriate and according to their discretion)
- 3. Study participants will also be offered a mailed summary of the trial findings
- 4. The findings will be posted on social media platforms such as Twitter and Facebook groups
- 5. The findings will be shared with charities and patient groups for dissemination within their patient and public networks
- 6. Patient representatives will also be invited to provide perspectives on how best to disseminate findings to study participants and other patient groups

## Intention to publish date

31/12/2026

# Individual participant data (IPD) sharing plan

The datasets generated during and/or analysed during the current study are/will be available upon request from Miss Sasha Smith (Imperial College London), sasha.smith@imperial.ac.uk. Data-sharing requests may be made outside the sponsor organisation and will be made under an appropriate data-sharing agreement.

# IPD sharing plan summary

Available on request

## **Study outputs**

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol file	version 12.0	14/01/2025	02/04/2025	No	No