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

Submission date
21/06/2023

Recruitment status
No longer recruiting

Registration date
30/06/2023

Overall study status
Completed

Last Edited
02/04/2025

Condition category
Nutritional, Metabolic, Endocrine

[X] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[_] 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

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Additional identifiers

ClinicalTrials.gov (NCT)
NCT03767478

Integrated Research Application System (IRAS)
237312

Protocol serial number
18HH4610

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 (μV), 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 (μV), 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

Primary study design
Interventional

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

Study type(s)
Treatment, Safety, Efficacy

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

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Revitive Medic Coach neuromuscular electrical stimulation

Primary outcome(s)
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).

Key secondary outcome(s)
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)

Secondary outcome measures
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 (μV) 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 (μV) 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

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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)

Secondary outcome measures
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 (μV) 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

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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)

Secondary outcome measures
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 (μV) 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

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 µV 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

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Sex
All

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
United Kingdom

England

Study participating centre
Imperial College Healthcare NHS Trust
Charing Cross Hospital
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Study participating centre
Mid and South Essex NHS Foundation Trust
Basildon University Hospital
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Sponsor information

Organisation
Imperial College London

ROR
https://ror.org/041kmwe10

Funder(s)

Funder type
Industry

Funder Name
Actegy Ltd

Results and Publications

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