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The utility of frequency-modulated electromagnetic neural stimulation as a third-line treatment in patients with painful diabetes-related peripheral neuropathy

Submission date
10/01/2023

Recruitment status
No longer recruiting

Registration date
16/01/2023

Overall study status
Ongoing

Last Edited
19/05/2025

Condition category
Nervous System Diseases

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[_] Record updated in last year

Plain English summary of protocol

Background and study aims
Diabetes mellitus (DM) is very common in the UK and globally and is a major healthcare challenge for the NHS. Diabetes UK announced that the number of people living with DM in the UK has more than doubled over the last 20 years, reaching 4.7 million in 2018, costing the NHS at least £10 billion a year, or 10% of the total NHS budget. The number of people living with DM is expected to reach 5 million in 2025 and 5.5 million in 2030, and the cost to the NHS is likely to increase significantly with this increased prevalence. Painful diabetes-related peripheral neuropathy (PDPN, damage to the nerves caused by high blood sugar levels) is a serious complication affecting 20-26% of patients with DM. PDPN has a major impact on quality of life, mood, sleep and relationships. This study aims to evaluate the clinical and cost-effectiveness of FREMS (frequency rhythmic electrical modulated system) in adults with PDPN.

Who can participate?
Patients aged 18 years and over with diabetes mellitus and neuropathic pain affecting both feet for at least 3 months or taking pain medication for neuropathic pain for at least 3 months

What does the study involve?
Participants are randomly allocated to receive 10 sessions of either transcutaneous electrical nerve stimulation (TENS) or FREMS treatment for 35 minutes each session. Follow-up is then up until 6 months.

What are the possible benefits and risks of participating?
The researchers do not expect any safety issues or risks for the participants. The only risk associated with either intervention is in the potential for soreness at the point of application of the adhesive patches during and shortly after treatment; this risk remains the same for both arms. Offering the study to potential participants may prolong the clinic visit. The time taken for patients to receive their treatment can also be deemed as a potential burden but this additional time was felt to be within acceptable limits by patients and patient society representatives. Both

treatments could give some pain relief to patients. Participants will have the potential opportunity to try a new therapy before it is generally available.

Where is the study run from?
University of Birmingham (UK)

When is the study starting and how long is it expected to run for?
January 2022 to February 2027

Who is funding the study?
National Institute for Health and Care Research (NIHR) (UK)

Who is the main contact?
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Contact information

Type(s)
Scientific

Contact name
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Additional identifiers

Integrated Research Application System (IRAS)
316524

Central Portfolio Management System (CPMS)
53965

National Institute for Health and Care Research (NIHR)
133599

Protocol serial number
Grant Code:

Study information

Scientific Title
The utility of frequency-modulated electromagnetic neural stimulation as a third-line treatment in patients with painful diabetes-related peripheral neuropathy: a randomised controlled trial

Acronym
FREMS-PDPN

Study objectives
In patients with painful diabetes-related peripheral neuropathy (PDPN), frequency-modulated electromagnetic neural stimulation (FREMS) added to standard care as a third-line treatment (or higher) is superior to standard care in terms of reducing pain, improving sleep, improving quality of life (QoL) and reducing the use of medications, especially opioids.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 28/11/2022, London-Bromley Research Ethics Committee (Temple Quay House, 2 The Square, Temple Quay, Bristol, BS1 6PN, UK; +44 (0)2071048118, +44 (0)2071048140, +44 (0) 2071048016; bromley.rec@hra.nhs.uk), ref: 22/LO/0683

Study design
Randomized; Interventional; Design type: Treatment, Device

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Painful diabetes-related peripheral neuropathy

Interventions
Design: A pragmatic, multi-centre, two-arm, parallel-group, double-blind, sham-controlled, randomised trial with an internal pilot.

Target population: 356 adults with PDPN for ≥3 months with significant pain (mean pain Numerical Rating Scale [NRS] ≥4 for ≤4 weeks prior to randomisation) despite trying ≥2 different classes of PDPN medications.

Setting: NHS Trusts with PDPN services and aligned primary care and podiatry services.

Sub-study: Aimed at ensuring that there is no worsening sensory dysfunction with the trial interventions. The sub-study will also look for different responder rates in relation to the quantitative sensory testing (QST) phenotype. The substudy will perform QST using the validated and standardised German Research Network on Neuropathic Pain (DFNS) protocol, which also has validated age and gender normative values

Treatment allocation: Participants will be individually randomised on a 1:1 basis between FREMS and transcutaneous electrical nerve stimulation (TENS) via a secure, online randomisation

system based at Birmingham Clinical Trials Unit. A minimisation algorithm will be used within the randomisation system to ensure equal distribution.

Screening visits: The research team will take pre-screening consent and assess partial eligibility. Participants will be asked to complete a 7-day pain diary in order to confirm trial suitability. The patient will complete a pain diary at home via their personal device.

Baseline visit: If the patient is eligible to take part, the research team will take full trial informed consent, and complete outcome assessments and questionnaires with them at a baseline visit. The research team will record participants' personal details, medical history and current medication for randomisation. At randomisation trial treatment will be allocated, and started as soon as is practical for the participant.

Treatment phase: 10 x 35-minute sessions over a 2-week period.

Follow-up: Patients will be followed up at 3 and 6 months post-randomisation. During these visits patients will be asked to repeat some of the questionnaires and outcome assessments completed at the baseline visit. Patients will complete the daily pain diary via text message /email for the duration of the trial from pre-screening to 6-month follow-up.

Statistical analysis and sample size: 356 patients will be recruited in total. Up to 100 of these patients will take part in the QST sub-study. The justification for the sample size is based on the placebo response from RCTs in PDPN which is estimated to be 1.4 (95% CI 1.2 to 1.6) points reduction in pain severity based on NRS. To detect a mean difference of 0.6 points between groups at 3 months using the standard method of difference between means using a two-sided t-test and assuming a standard deviation of 1.65 (effect size 0.36) with 90% power and a type I error rate of 5%, a total of 160 participants per group will need to be randomised, 320 in total. Assuming and adjusting for a 10% attrition rate, 356 participants will need to be recruited (178 per group).

Intervention Type
Device

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Frequency-Modulated Electromagnetic Neural Stimulation (FREMS) device

Primary outcome(s)
7-day average 24-hour pain on an 11-point NRS scale (0 = no pain and 10 = worst pain imaginable) measured at 3 months post-randomisation

Key secondary outcome(s))
Current secondary outcome measures as of 15/04/2025:
Clinical:
1. 7-day average 24-hour pain measured on an 11-point NRS scale at the end of treatment and 6 months
2. Disease-specific quality of Life (QoL) measured using the Neuropathic Pain Impact on Quality-of-Life Questionnaire (NePIQoL) at 3 and 6 months
3. Treatment success (measured as a 30% reduction in 7-day average 24-hour pain scores) at the

end of treatment, 3 and 6 months
4. Treatment success (measured as a 50% reduction in 7-day average 24-hour pain scores) at the end of treatment, 3 and 6 months
5. Area Under the Curve (AUC) for the daily NRS pain scores over the study period (from baseline to 3 months and from baseline to 6 months)
6. Pain interference with function measured using the Brief Pain Inventory-Diabetic Peripheral Neuropathy (BPI-DPN) at 3 and 6 months
7. Depression measured using the Beck Depression Inventory at 3 and 6 months
8. Sleep quality measured using the Pittsburgh Sleep Quality Index (PSQI) at 3 and 6 months
9. Pain intensity measured using the Neuropathic Pain Symptom Inventory (NPSI) at the end of treatment, 3 and 6 months.
10. Participant ratings of overall improvement, assessed by the Patients' Global Impression of Change (PGIC) and Clinician Global Impression of Change (CGIC) with a 7-point Likert scale at the end of treatment, 3 and 6 months
11. Changes to pain medications (frequencies and dosages) measured using patient-reported outcomes/clinical examination and interview with the patient at 3 and 6 months
12. Patient perception of their treatment arm, documented on the end-of-treatment participant case report form (CRF) by the patient. The patient has the option to select if they think they received FREMS or TENS. Measured at the end of the treatment phase.

Cost-effectiveness:
1. Health-related QoL assessed by the EQ-5D-5L at 6 months
2. Health resource use measured using the Health Economic Questionnaire at 3 and 6 months
3. Cost per quality-adjusted life year (QALY) gained over 6 months measured using the Health Economic Questionnaire

Subgroup outcomes:
Changes in overall PDPN and overall quality of life measured using the Neuropathic Pain Symptom Inventory (NPSI) questionnaire mean total score and mean subscores (burning, pressing, paroxysmal and evoked pain, paresthesia/dysesthesia) at end of treatment, 3 and 6 months

Safety:
1. Frequency and proportion of adverse events documented from the start of treatment until 7 days after the last treatment dose and will be reviewed for any changes in decreased pain and overall quality of life
2. Frequency of serious adverse events documented from the first treatment dose until the 6-month follow-up, to assess the safety of treatment/patient tolerance and overall treatment success/burden

Previous secondary outcome measures:
Clinical:
1. 7-day average 24-hour pain measured on an 11-point NRS scale at the end of treatment and at 6 months
2. Disease-specific quality of Life (QoL) measured using the Neuropathic Pain Impact on Quality-of-Life Questionnaire (NePIQoL) at 3 and 6 months
3. Treatment success (measured as a 30% reduction in 7-day average 24-hour pain scores) at end of treatment, 3 months and 6 months
4. Treatment success (measured as a 50% reduction in 7-day average 24-hour pain scores) at end of treatment, 3 months and 6 months.
5. Area Under the Curve (AUC) for the daily NRS pain scores over the study period (from baseline to 3 months and from baseline to 6 months)

6. Pain interference with function measured using the Brief Pain Inventory-Diabetic Peripheral Neuropathy (BPI-DPN) at 3 months and 6 months
7. Depression measured using the Beck Depression Inventory at 3 and 6 months
8. Sleep quality measured using the Pittsburgh Sleep Quality Index (PSQI) at 3 and 6 months
9. Participant ratings of overall improvement, assessed by the Patients' Global Impression of Change (PGIC) and Clinician Global Impression of Change (CGIC) with a 7-point Likert scale at end of treatment, 3 months and 6 months
10. Changes to pain medications (frequencies and dosages) measured using patient-reported outcomes/clinical examination and interview with the patient at 3 and 6 months
11. Patient perception of their treatment arm, documented on the end-of-treatment participant case report form (CRF) by the patient. The patient has the option to select if they think they received FREMS or TENS. Measured at the end of the treatment phase.

Cost-effectiveness:
1. Health-related QoL assessed by the EQ-5D-5L at 6 months
2. Health resource use measured using Health Economic Questionnaire at 3 and 6 months

Subgroup outcomes:
Changes in overall PDPN and overall quality of life measured using the Neuropathic Pain Symptom Inventory (NPSI) questionnaire mean total score and mean subscores (burning, pressing, paroxysmal and evoked pain, paresthesia/dysesthesia) at end of treatment, 3 months and 6 months

Safety:
1. Frequency and proportion of adverse events documented from the start of treatment until 7 days after the last treatment dose and will be reviewed for any changes in decreased pain and overall quality of life
2. Frequency of serious adverse events documented from the first treatment dose until the 6-month follow-up, to assess the safety of treatment/patient tolerance and overall treatment success/burden

Completion date
28/02/2027

Eligibility

Key inclusion criteria
Current inclusion criteria as of 15/04/2025:
1. Aged ≥18 years
2. Neuropathic pain affecting both feet for ≥3 months or taking pain medication for neuropathic pain for ≥3 months
3. Mean pain score ≥4 on the daily NRS ≤4 weeks prior to randomisation
4. Douleur Neuropathique 4 (DN-4) questionnaire score ≥4/10 at screening to confirm the diagnosis of bilateral distal symmetrical neuropathic pain [70]
5. Diabetes-related neuropathy based on the Michigan Neuropathy Screening Instrument (MNSI) (MNSI questionnaire scored ≥7 or examination scored >2) [71, 72]
6. HbA1c <108 mmol/mol or 12% taken (within last 2 months).
7. Have tried at least two anti-neuropathic drugs from two different classes for PDPN
8. Willing and able to comply with the study schedule and be available for the treatment duration
9. Able to give written informed consent

Previous inclusion criteria:
1. Aged ≥18 years
2. Neuropathic pain affecting both feet for ≥3 months or taking pain medication for neuropathic pain for ≥3 months
3. Mean pain score ≥4 on the daily NRS for 1 week prior to randomisation
4. Douleur Neuropathique 4 (DN-4) questionnaire score ≥4/10 at screening to confirm the diagnosis of bilateral distal symmetrical neuropathic pain
5. Diabetes-related neuropathy based on the Michigan Neuropathy Screening Instrument (MNSI) (MNSI questionnaire scored ≥7 or examination scored >2)
6. HbA1c <108 mmol/mol or 12% (within the last 2 months)
7. Have tried at least two drugs from two different classes for PDPN
8. Willing and able to comply with the study schedule and be available for the treatment duration
9. Able to give written informed consent

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Key exclusion criteria
Current exclusion criteria as of 15/04/2025:
1. Non-diabetic neuropathies
2. Currently using TENS for PDPN
3. History of epilepsy
4. Other painful medical conditions where the pain is significantly more severe than their PDPN pain (patients will not be excluded if the pain is transient in nature)
5. Major amputations of the lower limbs
6. Active diabetic foot ulcers
7. Active malignancy
8. Patient has a pacemaker, defibrillator or neurostimulator
9. Pregnancy

Previous exclusion criteria:
1. Non-diabetic neuropathies
2. Currently using TENS for PDPN
3. History of epilepsy
4. Other painful medical conditions where the pain is significantly more severe than their PDPN pain (patients will not be excluded if the pain is transient in nature)
5. Major amputations of the lower limbs
6. Active diabetic foot ulcers
7. Diagnosed malignancy

8. Pacemakers, defibrillator or neurostimulator
9. Pregnancy

Date of first enrolment
31/01/2023

Date of final enrolment
28/02/2026

Locations

Countries of recruitment
United Kingdom

England

Wales

Study participating centre
The Walton Centre
Lower Lane
Fazakerley
Liverpool
United Kingdom
L9 7LJ

Study participating centre
Heartlands Hospital
Bordesley Green East
Bordesley Green
Birmingham
United Kingdom
B9 5ST

Study participating centre
Ipswich Hospital
Heath Road
Ipswich
United Kingdom
IP4 5PD

Study participating centre

Royal Hallamshire Hospital
Glossop Road
Sheffield
United Kingdom
S10 2JF

Study participating centre
George Eliot Hospital
College Street
Nuneaton
United Kingdom
CV10 7DJ

Study participating centre
Kings College Hospital
Mapother House
De Crespigny Park
Denmark Hill
London
United Kingdom
SE5 8AB

Study participating centre
Manchester Diabetes, Endocrine and Metabolism Centre
Manchester Royal Infirmary
Cobbett House
Oxford Road
Manchester
United Kingdom
M13 9WL

Study participating centre
Minerva Health Centre
Lancashire and South Cumbria NHS Foundation Trust
Sceptre Way
Walton Summit
Preston
United Kingdom
PR5 6AW

Study participating centre

University Hospital of Wales
Cardiff and Vale University Local Health Board
Woodland House
Cardiff
United Kingdom
CF14 4HH

Study participating centre
Hywel Dda University Lhb
Corporate Offices, Ystwyth Building
Hafan Derwen
St Davids Park, Jobswell Road
Carmarthen
United Kingdom
SA31 3BB

Sponsor information

Organisation
University of Birmingham

ROR
https://ror.org/03angcq70

Funder(s)

Funder type
Government

Funder Name
NIHR Evaluation, Trials and Studies Co-ordinating Centre (NETSCC)

Results and Publications

Individual participant data (IPD) sharing plan
The final dataset will be available to members of the TMG and co-applicant group who need access to the data to undertake the final analyses.
Requests for data generated during this study will be considered by BCTU. Data will typically be available 6 months after the primary publication unless it is not possible to share the data.
Only scientifically sound proposals from appropriately qualified Research Groups will be

considered for data sharing. The request will be reviewed by the BCTU Data Sharing Committee in discussion with the CI and, where appropriate (or in absence of the CI) any of the following: the Trial Sponsor, the TMG, and the TSC.
A formal Data Sharing Agreement may be required between respective organisations once the release of the data is approved and before data can be released. Data will be fully de-identified (anonymised) unless the Data Sharing Agreement covers the transfer of participant-identifiable information. Any data transfer will use a secure and encrypted method.

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			26/07/2023	No	No
Study website	Study website	11/11/2025	11/11/2025	No	Yes