UNIVERSITY OF BIRMINGHAM | BCTU

FREMS-PDPN

TRIAL PROTOCOL

FREMS-PDPN

The Utility of Frequency-Modulated Electromagnetic Neural Stimulation (FREMS) as a Third Line Treatment in Patients with Painful Diabetes-Related Peripheral Neuropathy: A Randomised Controlled Trial

This protocol has regard for the HRA guidance and is compliant with the SPIRIT guidelines (2013)

Version Number: V3.0

Version Date: 16th January 2023

Protocol amendments

The following amendments and/or administrative changes have been made to this protocol since the implementation of the first approved version.

Amendment number	Date of amendment	Protocol version number	Type of amendment	Summary of amendment
01	16-01-2023	3	Non-substantial	ISRCTN number inserted Trial logo inserted TSC members inserted DMC member inserted Trial social media address inserted Routine biochemistry requirement at baseline removed QST requirement at 6 month follow up removed

Funding and support in kind

	Financial and non-financial support given:
National Institute for Health Research (NIHR)	£988,572.17
Funding scheme	Health Technology Assessment (HTA)
Funder's reference number	NIHR133599

The Funder of the trial has had no role in the trial design, data collection, data analysis or data interpretation. This project is funded by the NIHR HTA Programme project reference 133599. The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care.

Chief Investigator (CI) signature page

As Chief Investigator, I confirm that I have read and agree with the following protocol, and that I will conduct the trial in compliance with the version of this protocol approved by the REC and any other responsible organisations.

I agree to ensure that the information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as stated in this and any subsequent approved protocol will be explained.

Trial name:	FREMS-PDPN
Protocol version number: Protocol version date:	Version: 3.0 16.01.2023
CI name:	Dr Bernhard Frank
Signature and date:	_____

Sponsor statement

Where the University of Birmingham takes on the sponsor role for protocol development oversight, the signing of the IRAS form by the sponsor will serve as confirmation of approval of this protocol.

Compliance statement

This protocol describes the FREMS-PDPN trial only. The protocol should not be used as a guide for the treatment of people not taking part in the FREMS-PDPN trial.

The trial will be conducted in compliance with the approved protocol, the UK Policy Framework for Health and Social Care Research, Data Protection Act 2018 and the Principles of Good Clinical Practice (GCP) as set out in the UK Statutory Instrument (2004/1031) and subsequent amendments thereof.

Every care has been taken in the drafting of this protocol, but future amendments may be necessary, which will receive the required approvals prior to implementation.

Principal Investigator (PI) signature page

As Principal Investigator, I confirm that the following protocol has been agreed and accepted, and that I will conduct the trial in compliance with the approved protocol where this does not compromise participant safety.

I agree to ensure that the information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

Trial name:	FREMS-PDPN
Protocol version number: Protocol version date:	Version: 3.0 16th January 2023
PI name:	
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ADMINISTRATIVE INFORMATION

Reference Numbers	
Sponsor number	RG_20-108
ISRCTN reference number	11665378
IRAS reference number	316524

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ABBREVIATIONS

Abbreviation	Term
AE	Adverse Event
AUC	Area Under the Curve
BCTU	Birmingham Clinical Trials Unit
BPI-DPN	Brief Pain Inventory – Diabetic Painful Neuropathy
CGIC	Clinician Global Impression of Change 7 item Likert Scale
CI	Chief Investigator
CRF	Case Report Form
DCF	Data Clarification Form
DFNS	German Research Network on Neuropathic Pain
DM	Diabetes Mellitus
DMC	Data Monitoring Committee
DN4	Douleur Neuropathique en 4 questions
EQ-5D-5L	EuroQol Five Dimensions Five Levels
FREMS	Frequency-Modulated Electromagnetic Neural Stimulation
GCP	Good Clinical Practice
HbA1c	Haemoglobin A1c - Measurement of glucose in haemoglobin
HRA	Health Research Authority
ICF	Informed Consent Form
ISF	Investigator Site File
MTA	Medical Technology Appraisal
MNSI	Michigan Neuropathy Screening Instrument
NePIQoL	Neuropathic Pain Impact on Quality of Life Questionnaire
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NPSI	Neuropathic Pain Symptom Inventory
NRS	Numerical Rating Scale

PDPN	Painful Diabetes-related Peripheral Neuropathy
PGIC	Patient Global Impression of Change 7 item Likert Scale
PI	Principal Investigator
PICs	Participant Identification Centres
PIS	Participant Information Sheet
PPI	Patient Public Involvement
PSQI	Pittsburgh Sleep Quality Index
QALY	Quality Adjusted Life Year
QOL	Quality of life
QST	Quantitative Sensory Testing
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RGT	University of Birmingham Research Governance Team
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCS	Spinal Cord Stimulation
SD	Standard Deviation
TcPO2	Transcutaneous Oxygen Pressure
TcPCO2	Transcutaneous Carbon Dioxide
TENS	Transcutaneous Electrical Nerve Stimulation
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
UoB	University of Birmingham
VAS	Visual Analogue Scale

TRIAL SUMMARY

Title

The Utility of Frequency-Modulated Electromagnetic Neural Stimulation (FREMS) as a Third Line Treatment in Patients with Painful Diabetes-Related Peripheral Neuropathy (PDPN): A Randomised Controlled Trial (FREMS-PDPN)

Aim

The aim of the trial is to evaluate the clinical and cost-effectiveness of FREMS for adults with PDPN.

Objectives

The primary objective is to evaluate the efficacy of FREMS in the reduction of 7 day mean pain score at 3 months.

Secondary objectives:

1. To evaluate the impact of FREMS on sleep, quality of life, mood, and medication use.
2. To assess safety and describe adverse and serious adverse events.
3. To evaluate the cost-effectiveness of FREMS in PDPN.
4. To explore if patient phenotypes (demography, diabetes type, type of pain, mood, sleep and quantitative sensory testing profiles) predict response to treatment.

Trial design

A pragmatic, multi-centre, 2-arm, parallel group, double blind, sham controlled, randomised trial with internal pilot.

Participant population and sample size

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

Setting

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

Eligibility criteria

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 one 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 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.

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

Interventions

FREMS + standard care vs Transcutaneous electrical nerve stimulation (TENS) + standard care

Outcome measures

Primary outcome:

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.

Secondary outcomes:

Clinical:

1. 7-day average 24-hour pain on an 11-point NRS scale (0 = no pain and 10 = worst pain imaginable) measured at the end of treatment and at 6 months.
2. Neuropathic Pain Impact on Quality-of-Life Questionnaire (NePIQoL) as a measure of disease specific quality of Life (QoL) 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. Brief Pain Inventory-Diabetic Peripheral Neuropathy (BPI-DPN) as a measure of pain interference with function total score at 3 months and 6 months.
7. Beck Depression Inventory as a measure of depression at 3 and 6 months.
8. Pittsburgh Sleep Quality Index (PSQI) as a general measure of sleep quality at 3 months and 6 months.
9. Patient (PGIC) and Clinician (CGIC) Global Impression of Change at end of treatment, 3 months and 6 months.
10. Changes to pain medications (frequencies and dosages) at 3 and 6 months.
11. Patient perception of their treatment arm at the end of the treatment phase.

Cost Effectiveness:

1. Health-related QoL at 6 months assessed by the EQ-5D-5L
2. Health resource use at 3 and 6 months.

Subgroup outcomes:

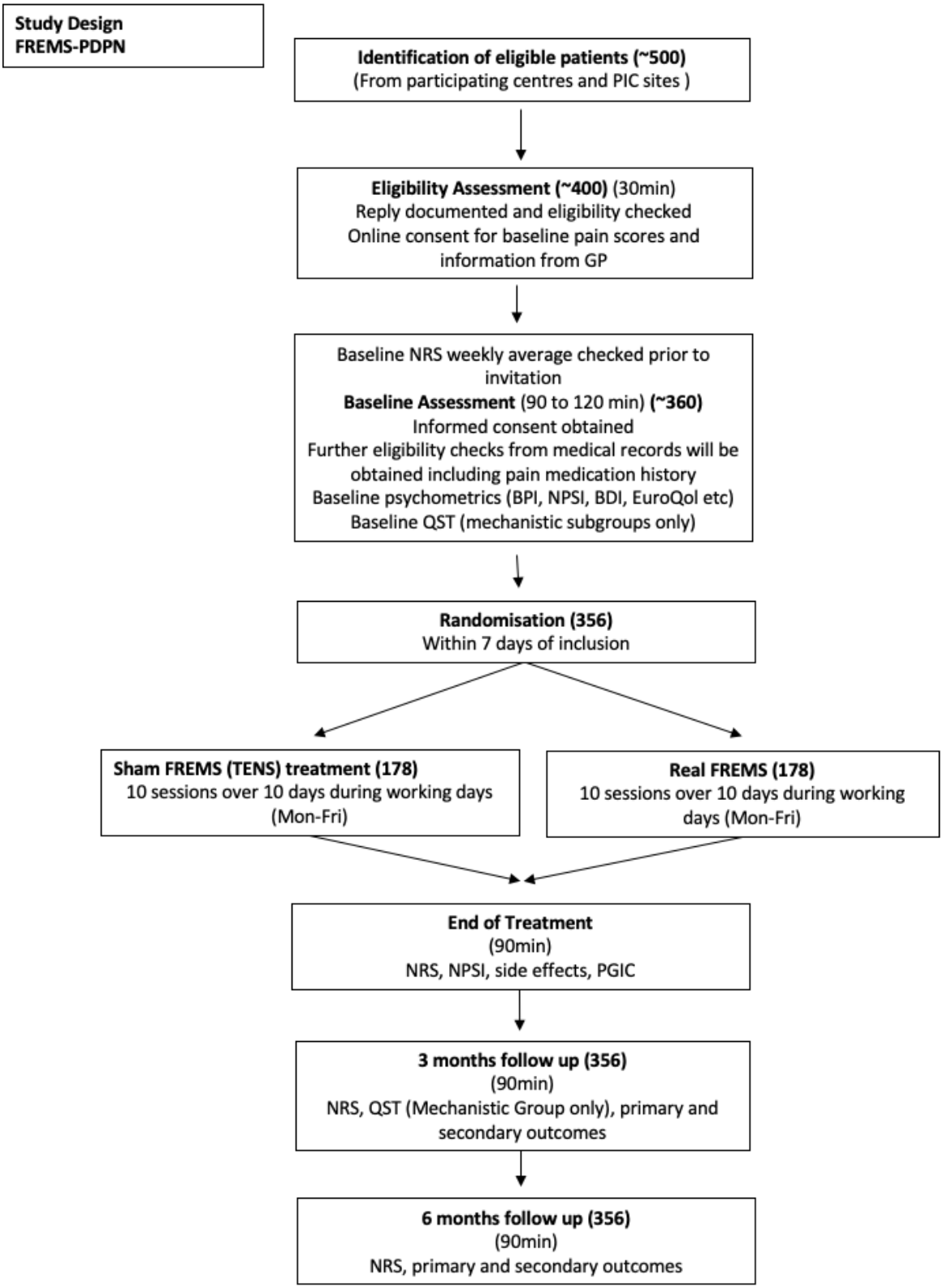
Neuropathic Pain Symptom Inventory (NPSI) questionnaire will be used for subgroup analysis relating pain phenotype to treatment response. In particular, these outcomes will be evaluated:

1. NPSI mean total score and mean subscores (burning, pressing, paroxysmal and evoked pain, paresthesia/dysesthesia) at end of treatment, 3 months and 6 months.

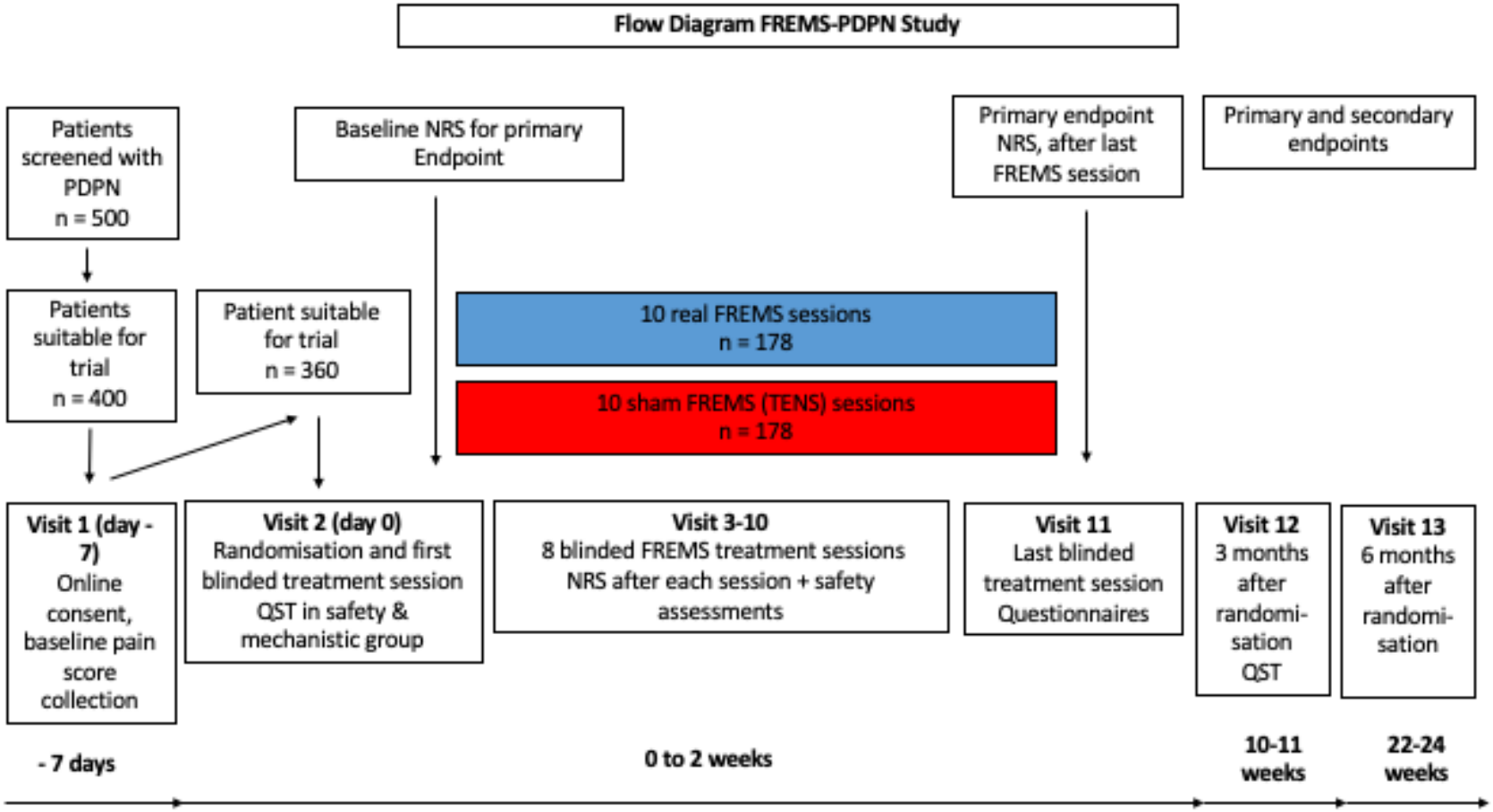
Safety:

1. Frequency and proportion of Adverse Events.
2. Frequency of Serious Adverse Events.

TRIAL SCHEMA



TRIAL FLOW DIAGRAM



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1. BACKGROUND AND RATIONALE

1.1. Background

Diabetes Mellitus (DM) is very common in the UK and globally and is a major health care 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 [1]. 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) is a serious complication affecting 20-26% of patients with DM [2, 3]. Research utilising the Clinical Practice Research Database showed that the incidence of PDPN was 17.8 per 100,000 person-years (95% confidence interval 17.4–18.2), which the authors acknowledge is likely to be an underestimate as this condition is likely to be underdiagnosed in primary care [4]. PDPN is associated with higher health care costs due to hospitalisations and outpatient visits and impaired work productivity [5]. In a UK study, the annual in-patient days ranged from 2.6-6.4 days in patients with PDPN and the number of GP contacts over 6 weeks was increased by 0.6-1.4 times. The mean annual health care costs per patient with PDPN in the UK was £2,511 [5, 6]. With an increasing prevalence of DM, the prevalence and burden of PDPN is likely to increase further over the next decade, which will pose a major treatment and financial challenge [7, 8].

PDPN has a major negative impact on quality of life (QoL). PDPN causes burning, deep aching, “electric shock” like, lancinating (“stabbing or knife like”) pains; pain generated by contact with day-time clothes and bedclothes (allodynia); dysaesthesic and soldering pain on walking often described as “walking barefoot on marbles”, or “walking barefoot on hot sand”; sensations of heat or cold in the feet; persistent achy feeling in the feet and cramp-like sensations in the legs [8, 9]. With advanced disease, the pain can extend above the feet and may involve the whole of the legs, and when this is the case there is often upper limb involvement also. Moderate-to-severe unremitting lower limb pain is present in over 70% of sufferers [3, 10] and causes insomnia, poor QoL, unemployment, and depression [11-14].

The mainstay of treatment for PDPN is pharmacotherapy [15]. Recent National Institute for Health and Social Care Excellence (NICE) guidance (173) [16] recommends a choice of amitriptyline, duloxetine, pregabalin or gabapentin as initial treatments. There is moderate evidence for the efficacy of each drug based on Cochrane reviews [17-20] and meta-analyses [21-23], but the best any monotherapy achieves is 50% pain relief in 50% of patients [16]. Inadequate dose titration occurs due to accompanying side effects (nausea, sedation, dizziness, dry mouth, weight gain, falls) in 40% of people and treatment withdrawal is common [7, 9]. NICE recommends combination treatment if initial treatment is not effective (as in the majority of cases) [10]. However, as NICE points out, recommendations are not based on robust evidence as:

1) there are few well-designed head-to-head studies comparing the first line drugs and their combinations;
2) most studies were low grade with inadequate power, inappropriate endpoints and/or short duration of follow-up; and
3) many randomised controlled trials (RCTs) lacked appropriate health-related QoL measures including functionality and failed to measure the impact of drug-related adverse effects on health economics and QoL [10].

Beyond the above-mentioned therapies, there are no NICE recommended treatments due to “lack of consistent evidence of effectiveness…. or evidence of a higher risk of adverse effects”. Treatments that “should not be used” include: carbamazepine, cannabis sativa extract, capsaicin patch, imipramine, lacosamide, lamotrigine, levetiracetam, lidocaine (topical), morphine, nortriptyline,

oxcarbazepine, topiramate, tramadol (long-term use) and venlafaxine [16, 24]. The Neuropathic Pain Special Interest Group (NeuPSIG) of the International Association for the Study of Pain (IASP) recommended in 2015 several agents following a systematic review including tramadol, lidocaine patches, capsaicin 8% patches, strong opioids and botulinum toxin A as second and third line therapies for peripheral neuropathic pain (not specifically PDPN) but it classified the strength of the recommendations for all these agents as "Weak" [25].

Considering the difficulty of treating PDPN and that at least 50% of patients do not respond to treatments (i.e. experiencing persistent pain) recommended by the NICE guidelines [26], it is not surprising that the use of opioids is common in these patients (43%) [27]. This is despite a Cochrane systematic review casting doubt over morphine efficacy in chronic neuropathic pain [28] and the significant side effects associated with opioid use. More recent evidence suggested a role for spinal cord stimulation (SCS) as a possible treatment for PDPN that is refractory to "conventional" treatments [29, 30]. In a multi-centre RCT (n=60), visual analogue scale pain rating (VAS, ranging 0-100) improved from 73 to 31 in the intervention group (P<0.001) and remained the same in the control group (67 vs 67, P=0.97) over 6 months and SCS improved QoL [29]. The SENZA trial in PDPN published in 2015 using high frequency 10-kHz SCS in a non-blinded trial against conventional medical management showed a clinically significant improvement in pain (VAS reduction from 76 to 17 compared to 70 to 69 in the control group) and neurological examination after 6 months [30]. However, SCS is an invasive procedure that requires specialist expertise and is associated with several adverse events including infection and lead problems requiring surgery to resolve (4% per year of follow-up), as well as a single case fatality from a subdural haematoma as shown in a recent systematic review [31].

Hence there is a clear gap in the treatment pathway of patients with PDPN regarding a safe, non-invasive, clinically effective and cost effective third line (or higher) treatment that is safe with an acceptable adverse event profile. FREMS treatment may also have the potential to reduce the need for opioids and their associated risks. Treatment with a Frequency-Modulated Electromagnetic Neural Stimulation (FREMS) machine may be able to address this gap.

1.2. Trial rationale

HEALTH CARE NEED:

Treatment gap in PDPN management; the need for safe, non-invasive, effective and cost-effective treatments in patients not responding to NICE recommended treatments.

NHS NEED:

Reduce health care use (GP visits, hospital care, medications). Determine the cost effectiveness of the intervention.

EXPRESSED NEED:

Chronic pain is a previous themed NIHR funding call. The NICE Medical Technology Appraisal (MTA) A43 stated that FREMS in patients with PDPN can reduce pain and improve QoL but its place in therapy is uncertain.

SUSTAINED INTEREST AND INTENT:

With increasing DM prevalence in the UK, PDPN burden is likely to increase. There are no significant treatment advances on the horizon. The outcomes of this study will be relevant to the NHS for the foreseeable future.

SCIENTIFIC KNOWLEDGE:

The study will advance scientific knowledge related to PDPN management. The NICE MTA A43 in 2017 identified several gaps that will be addressed by this study.

Table 1: Gap: Answer

Knowledge gaps/uncertainties	**How FREMS-PDPN will address the gaps**
Lack of UK studies	FREMS-PDPN is based in the UK
Intended **place in therapy** is uncertain	FREMS-PDPN will assess the impact of FREMS treatment in a well-defined population: patients with PDPN who have significant persistent pain despite trying the first- and second-line treatments recommended by NICE.
No studies comparing FREMS with other available treatment options	FREMS-PDPN will examine FREMS as at least a third line treatment. There is no agreed or well established NICE recommended third line pharmacotherapy and hence the use of opioids and other treatment options is common. The control arm will be routine care + "sham" FREMS. The sham FREMS is standard low intensity high frequency TENS (Transcutaneous Electrical Nerve Stimulation). Hence treatment can be intensified in the control arm as per the treating clinician guidance and patient wishes.
Current evidence is limited in quality	FREMS-PDPN will improve the quality of the evidence for FREMS by using a well-defined population, larger sample size, more detailed assessments including economic evaluation and importantly having a double-blind approach. Previous RCTs were not adequately blinded as the control arms did not receive electrical current; and many patients can feel this current and hence the lack of this feeling will alert the patient and assessor to treatment allocation. In FREMS-PDPN patients in both arms will be able to feel an electrical current.
Current evidence is limited in quantity	FREMS-PDPN will be considerably larger than previous FREMS RCTs and similar in size to other pharmacological trials for PDPN.
Unclear impact on medications use	FREMS-PDPN will assess changes in anti-neuropathic drug treatment and dosing, including opioids, in detail.

Lack of economic evaluation	FREMS-PDPN will include a robust economic evaluation and cost effectiveness analysis.

Some of the secondary outcomes will also explore personalised treatment approaches.

BUILDING ON EXISTING WORK:

This includes 2 non-UK RCTs, and 3 studies conducted by the investigator group including 2 uncontrolled studies and 1 pilot RCT.

PROSPECTS FOR CHANGE:

We will liaise with NICE when the results of this definitive trial are available. This work will address the gap identified by the 2017 NICE MTA which were reiterated in a teleconference with NICE, organised by BHR pharmaceuticals, in May 2019.

1.3. Justification for design

FREMS-PDPN is a pragmatic, multi-centre, 2-arm, parallel group, double blind, sham controlled, randomised trial of patients with PDPN (defined as pain severity of ≥ 4 on 11-point numerical rating scale [NRS] measuring 24-hour pain scores [0 to 10] averaged over the last 7 days) who have not responded to at least two different classes of neuropathic pain medications as per NICE guidance. The RCT will have an internal pilot phase with stop/go criteria. The patients will be randomised in a 1:1 ratio to either FREMS + standard care or TENS + standard care. The primary outcome (24-hour pain using NRS averaged over the last 7 days) is measured at 3 months post-randomisation and the final follow up is at 6 months post-randomisation The administering team, the participant and all researchers will be blinded to treatment allocation.

Our hypothesis is that in patients with PDPN, 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 QoL and reducing the use of medications, especially opioids. Standard care usually includes the use of one or more of the medications listed in Section 1.1 and in some patients it will include referral to neuropathy clinics, diabetes clinics or pain clinics.

Why no washout period?

As both FREMS and TENS will be used in addition to standard care, there is no washout period of any medications before randomisation.

Why allowing standard care in both arms?

As part of standard care, treatment might be escalated or reduced at the discretion of the patient and the treating clinician. This could reduce the efficacy of the intervention. However, we did not observe this within the FREMS-TOP pilot study with a population that had already tried two classes of medications because the up titration of medications is limited by significant side effects. Furthermore, within the FREMS-PDPN trial, data will be collected on changes in medications. Allowing standard care in both arms will also facilitate recruitment as it does not restrict patient access to treatment. It would be challenging ethically to leave patients in significant pain without giving them the opportunity to receive treatment. This was echoed by our Patient and Public Involvement (PPI) group, who highlighted the importance of the continuation of standard care to facilitate recruitment and randomisation to the study.

Why patients who have failed two pharmacological treatments?

We will assess FREMS in patients who have already failed two pharmacological treatments with different modes of action because there is currently no agreement about the best third line

treatment. At least 50% of patients will require third line treatment. High quality evidence is needed to guide treatments for these patients.

Why not active pharmacotherapy as the control arm?

We chose to have a design of FREMS vs TENS rather than a comparison with active pharmacotherapy due to the lack of consensus about the most appropriate third line treatment, and because we allow treating clinicians to escalate or deescalate treatment as they see necessary in both arms.

1.4. Justification for participant population

The eligibility criteria were chosen to facilitate recruitment of the appropriate target population, while excluding patients who have contradictions to FREMS as per the manufacturer information. The eligibility criteria are therefore designed to identify patients with PDPN who still have significant pain (mean pain intensity ≥4 on the NRS), consistent with previous trials in the field [26, 32]. The criteria exclude patients with causes of neuropathic pain other than diabetes. We did not restrict inclusion based on receiving opioids because previous studies (discussed above) showed a reduction in opioids use following FREMS and this will be an important outcome.

1.5. Justification of choice of intervention

FREMS is a non-invasive treatment modality for several chronic painful conditions. FREMS mechanisms

FREMS has multiple effects on vasculature that might contribute to its favourable effects on PDPN. FREMS has been shown to improve microvascular function measured using laser doppler [41, 57]. FREMS has also been shown to increase vascular endothelial growth factor and improve microcirculation and microvascular function in patients with DM [41, 42, 58]. In addition, FREMS improved cutaneous blood flow based on laser doppler flowmetry, and transcutaneous oxygen pressure ($TcPO^2$) and transcutaneous carbon dioxide ($TcPCO^{2)}$ [58, 59]. Furthermore, FREMS treatment has been shown to lower "neuronal hyperexcitability" in healthy people (based on the Hoffman reflex amplitudes) [60]. FREMS also improved sensory tactile perception, foot vibration perception and motor nerve conduction velocity when compared to placebo in a RCT in patients with DM [43].

1.5.1 FREMS vs. TENS

FREMS is different from TENS. TENS delivers mono- or bi-phasic electrical signals with a fixed frequency while FREMS delivers biphasic asymmetric electric sequences of negative pulses with double modulation (frequency and duration) [61]. This double modulation in FREMS is believed to have an advantage over the "predictable" TENS pulses by not allowing the adaptation observed with TENS [61-63]. Adaptation results in progressive desensitisation to stimulation [64]. A Cochrane systematic review showed that the quality of evidence for the use of TENS in neuropathic pain was very low and the authors were unable to reach any conclusion regarding TENS efficacy in patients with neuropathic pain [33]. On the other hand, in the only RCT to compare FREMS to TENS (in patients with myofascial pain syndrome), only FREMS reduced pain over 3 months [61].

1.5.2 NICE Medical Technology Appraisal 2017

In 2017, NICE published an MTA regarding the use of FREMS in patients with PDPN. This is the summary from the NICE MTA [65]:

- The innovative aspect of the technology is that it is designed to be a non-drug option for treating painful diabetic neuropathy, with a novel mechanism of action.
- The intended place in therapy is uncertain. It could be used in addition to, or in place of, current drug treatment options.
- The main points from the evidence summarised in this briefing are from 4 non-UK-based studies, consisting of 3 RCTs including 2 cross-over studies and 1 case-control study. The studies include

151 adult patients in an ambulatory care setting. They show that FREMS can reduce pain and improve QoL and neurovascular measures compared with sham FREMS in patients with PDPN.

- Key uncertainties around the evidence or technology are that there are no studies comparing FREMS with other available treatment options, and the current evidence is limited in quality and quantity. In addition, none of the studies were UK-based and changes to medication use and dosages in patients receiving FREMS were not well reported [43, 44].

The two RCTs that have been published, examined FREMS in the NICE MTA are summarised below in **Table 2** (https://www.nice.org.uk/advice/mib119/chapter/Clinical-and-technical-evidence). There have been no further published RCTs regarding FREMS in PDPN since the MTA was published in 2017.

Table 2: Summary of the FREMS RCTs in NICE MTA 2017.

Study: Bosi et al. (2005) (https://link.springer.com/article/10.1007/s00125-005-1734-2)	
Study size, design and location	31 adult patients with type 1 or type 2 DM and painful neuropathy. Randomised, double-blind crossover design. Italy.
Intervention and comparator(s)	PhysioFlog ETS 501 FREMS and placebo (sham treatment using the same device with no electrical stimulation) in 2 cycles of 10 treatments with each intervention in random sequence, with each series lasting no more than 3 weeks.
Key outcomes	After FREMS treatment there was a significant decrease in daytime and night-time pain scores and a significant increase in vibration perception across all recruited patients. These improvements persisted up to the final follow-up at 4 months. No significant differences were observed after placebo treatment. At 4 month follow-up, there were significant improvements in quality of life (SF-36).
Strengths and limitations	Randomised double-blind design. Funded in part by a research grant from Lorenz Biotech (the original manufacturer). Cross over design with short wash out and risk of carry over effect, small sample, blinding is limited as patients in the placebo group could not feel any "buzzing".
Study: Bosi et al. (2013) (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3563945/)	
Study size, design and location	110 adult patients with a diagnosis of type 1 or 2 DM with symptomatic neuropathy. RCT. Six sites across Italy, Germany and France.
Intervention and comparator(s)	Aptiva FREMS and placebo (sham treatment using the same device with no electrical stimulation).
Key outcomes	Night-time and daytime pain was significantly reduced in the intervention group up to 37 weeks after initial treatment. Total follow-up was 51 weeks. There was a significant increase in cold sensation threshold in the intervention group compared with the placebo group.
Strengths and limitations	Long follow-up. Randomised double-blind design. Large sample size. **Focused on mild neuropathy only**. Funded by Lorenz Lifetech. Some patients had very little pain (Pain score < 4) and the primary outcome is not based on pain (based on nerve conduction)

In addition to the 2017 NICE MTA, a teleconference with NICE organised by BHR pharmaceuticals in May 2019 concluded that:

1. There is a need for a UK study;
2. The study needs to be conducted in a well-defined population;
3. The study needs to address the place of FREMS in the treatment paradigm.

1.5.3 Feasibility and Pilot data

The two above-mentioned RCTs show that patients with PDPN can be randomised to FREMS vs sham FREMS, and that FREMS overall is efficacious in reducing pain and improving QoL in PDPN. Below we share 3 sets of data concerning the use of FREMS in routine care from the UK and the Netherlands and a pilot RCT using FREMS as a third line treatment modality.

1.5.4 Routine care data from Birmingham Heartlands Hospital, UK

Birmingham Heartlands Hospital has an established diabetes-related neuropathy clinic since 2012; some of the patients in this clinic have PDPN. The APTIVA FREMS unit was given to this clinic by BHR Pharmaceutical Ltd, who also covered the cost of the consumables. Patients with PDPN (N=23) who failed to respond to (or did not tolerate) at least two lines of pharmacotherapy (including the drugs recommended by NICE guidance) were offered FREMS. FREMS was delivered in the diabetes centre by a health care assistant over 10 consecutive out-patients sessions (excluding weekends) for 35 minutes each. Patients with contraindications to FREMS (e.g. epilepsy, implantable device) were excluded.

By 3 months, pain NRS and EQ-5D-5L VAS improved from mean±SD 8.4±1.4 to 6.2±3.0 and 57.5±10.6 to 72.5±3.5 respectively, which was maintained by 6 months. All 12 patients who were on opioids at baseline stopped them. Despite the lack of reimbursement for travel, none of the patients declined FREMS or missed any sessions (unpublished data).

1.5.5 Uncontrolled data from the Netherlands

These data are from Elisabeth-Tweesteden Hospital, Tilburg and Bethesda Diabetes Research Centre, Hoogeveen. This was an uncontrolled prospective study of patients with PDPN and persistent pain despite at least two lines of pharmacotherapy (including pregabalin or duloxetine or similar as per NICE guideline). The primary outcome was 50% reduction in pain scores at 1 and/or 3 months post-FREMS. In responders, FREMS was repeated every 4 months up to 12 months. FREMS was applied to both legs below the knees using 4 sets of electrodes per leg; the treatment consisted of 10 sessions of 35 minutes given over 14 days. Pain was assessed using the Neuropathic Pain Symptom Inventory (NPSI) and QoL was assessed using the EQ-5D-5L.

248 patients met the inclusion criteria; 56% male, average age 65 years old, and average diabetes duration 12.6 years. Before FREMS treatment, the average NPSI was 50±18. This improved after 1 and 3 months to 34±20 and 32±20 respectively ($p<0.001$ vs baseline). This improvement was maintained at 12 months ($p<0.001$). 50% decreases in NPSI scores (which is considered the ideal response) were seen in 80/248 (32.2%) at month 1 and in 87/248 (35.1%) at month 3. One third reduction in pain scores (which is considered clinically meaningful) occurred in 111 (44.8%) patients at month 1, and 123 (49.6%) at month 3.

The EQ-5D-5L VAS improved from 52.6±15.9 to 62.8±14.6 and 63.6±16.7% at months 1 and 3 respectively ($P<0.001$ vs baseline).

All of these improvements in pain scores, QoL and disability scores occurred in the context of a reduction of neuropathic pain medications over a 12 month period, including stopping opioids (unpublished data under peer review).

1.5.6 A single centre pilot RCT in Nuneaton, UK: The FREMS-TOP study [66]

This study aimed to randomise 35 patients; but recruitment was stopped early in April 2020 due to the COVID-19 pandemic. At closure, the study had randomised 25 patients and 22 had completed the study. This RCT included adults with either type 1 or type 2 DM, with neuropathic pain score ≥ 4 pain on NRS at screening and at randomisation despite receiving at least 2 of the below mentioned treatment options: duloxetine, pregabalin, gabapentin, amitriptyline, carbamazepine, phenytoin, tramadol, opioids. This RCT population is therefore similar to the population proposed in this protocol. Patients were randomised to FREMS + standard care vs standard care only. FREMS was delivered for 35 minutes/day for 10 days over 2 weeks excluding weekends.

Results: Over the 3 months follow up, patients randomised to FREMS + standard care had improvements in pain severity (based on SF-MPQ-2 and DN-4 questionnaire), QoL and insomnia, while patients randomised to standard care had no improvement in pain severity or insomnia and had worsening of QoL. Similarly, at 3 months the Patient Global Impression of Change (PGIC) at 3 months was greater in the intervention group compared to the controls (r=0.75, p=0.005).

1.5.7 Summary of the presented evidence

Taken together, the two published RCTs show that FREMS can reduce pain and improve QoL in patients with PDPN compared to sham FREMS, although these studies were small and included a wide range of patients with PDPN including those with mild disease which makes it difficult to determine where FREMS treatment can be used best (i.e. early vs late in the course of treatment). The two RCTs and pilot RCT show that recruitment and randomisation are feasible. The two health service evaluations show that FREMS is acceptable to patients with PDPN who fail to respond to two classes of medications as recommended by NICE, and that FREMS is associated with improvement in pain and QoL for up to 12 months in a real-life setting. The pilot RCT shows that FREMS is potentially beneficial in patients with PDPN as a third (or above) line treatment. All the studies and health service evaluations showed that the improvement in pain and QoL occurred in the context of a reduction in neuropathic pain medication including opioids.

1.6. Justification for choice of control arm

The control in this trial will be low intensity high frequency conventional TENS delivered in the same manner as FREMS (35 minutes for 10 days) using the same electrodes and device to the lower legs. TENS was chosen for multiple reasons:

1. <u>Blinding:</u>
   To enable a blinded study to be undertaken. Please see Section 6.7.
2. <u>TENS effects uncertain and short lived in PDPN</u>:
   A 2017 Cochrane systematic review in adults concluded that the effects of TENS in neuropathic pain were unclear due to the very low quality of evidence [33]. There were only two RCTs in PDPN in this systematic review [34, 35]. The RCT by Nabi et al delivered TENS to the lower limbs for 10 sessions, of 20 minutes each [36]. This RCT showed that the pain score based on NRS improved by 1 week but **returned to baseline by 3 months** post-treatment [36]; these results were similar to an older meta-analysis in patients with PDPN [35]. Other RCTs and systematic reviews also showed no effects for TENS in PDPN [35, 37]. Since the publication of the Cochrane review, another RCT has been published; it only included 5 patients with a study duration of 10 days [38]. In this RCT, the investigators used a cross-over design with a 1-week washout period which they considered to be enough in order not to have residual effects from TENS [38]. Hence, TENS is unlikely to produce meaningful reductions in pain scores by the primary outcome at 3 months and study end at 6 months considering the rapid onset and offset of conventional low intensity TENS [39].

Why low intensity high frequency TENS rather than other TENS types?

Low-intensity, high-frequency TENS (conventional TENS) at the site of pain produces "strong but comfortable TENS paraesthesia" [39]. This selectively activates large diameter non-noxious afferents to elicit segmental analgesia [39]. The mechanism of action results in rapid onset and offset of effects requiring TENS to be used whenever needed to achieve pain relief (even throughout the day) [40]. On the other hand, FREMS effects are likely to be due to improved endothelial function and microvascular flow, increased vascular endothelial growth factor and improvements in several aspects of neuropathy as detailed in Section 1.4.2 below [41-44]. These differences in mechanisms are the likely cause for the different duration in pain relief and extended carry over effect from FREMS. Hence the use of conventional low intensity high frequency TENS is unlikely to affect the study outcomes and at the same time will aid blinding.

1.7. Justification of choice of primary outcome

The primary outcome is the difference in the 7-day mean 24-hour pain score (evaluated at participant level) on an 11-point NRS scale (0 = no pain and 10 = worst pain imaginable) between arms measured at 3 months post randomisation. The 7-day mean 24-hour NRS is considered the gold standard for the assessment of neuropathic pain and has been employed in almost all well-designed neuropathic pain studies over the past 10 years [45-47]. Changes in the 7-day mean NRS were used by the international IMMPACT recommendations and others to determine and validate the clinically important differences in pain intensity [45, 48]. IMMPACT is the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials, which included a consensus statement from 40 participants from universities, governmental agencies, a patient organisation, and the pharmaceutical industry.

NICE clinical guidance 173 also recommended the use of the 11-point NRS in neuropathic pain trials in the research recommendations section. The European Medicine Agency also recommends the use of the NRS in pain trials [49]. The NRS will be collected daily throughout the study period via text messages or via email (as suggested by the PPI group), but only the average of the 7 days prior to the 3 months-time point will be used for the primary outcome analysis. The NRS daily pain score will be facilitated by the University of Birmingham's ReDCAP system via either email or the third-party text message provider FireText.

We chose the primary outcome to be at 3 months with a longer follow up at 6 months as this is consistent with other trials in the field of PDPN which were between 6-12 weeks duration [32, 50-55]. The previous FREMS RCTs, the health service evaluations, the pilot RCTs, and our clinical experience with using the device suggests that the treatment effect starts wearing off around 4-6 months after the initial FREMS treatment. In our clinical experience, patients contact us asking for another FREMS treatment session 4-6 months after their initial treatment. The Outcome measures of Rheumatology OMERCAT-12 recommended using 6 months follow up as minimal duration in chronic pain trials [56].

2. AIMS AND OBJECTIVES

2.1 Internal pilot objectives

1. To assess the feasibility of identifying eligible patients.
2. To assess the acceptability of randomisation to receive the intervention or not.
3. To determine if the pilot phase should continue to a full trial.

The stop/go criteria will be assessed after 6 months of recruitment. This is described in detail in section 8.1.

2.2 Main trial objectives

2.2.1 Clinical objectives

1. To evaluate the efficacy of FREMS using 11-point NRS 24-hour pain scores (0 to 10) averaged over the last 7 days before the 3 months follow up assessment (Primary objective).
2. To evaluate the impact of FREMS on other efficacy outcomes including sleep, QoL, mood and medication use at the 3 months follow up assessment.

2.2.2 Economic objectives

To evaluate the cost-effectiveness of FREMS in patients with PDPN.

2.2.3 Safety objectives

To describe (Serious) Adverse Events data (summarised both at patient level and event level).

2.2.4 Subgroup study objectives (exploratory objectives)

To conduct a subgroup analysis to investigate if patient phenotypes (demography, diabetes type, type of pain, mood, sleep and quantitative sensory testing profiles) predict response to treatment.

3. TRIAL DESIGN AND SETTING

FREMS-PDPN is a pragmatic, multi-centre, 2-arm, parallel group, double blind, sham controlled, randomised trial of patients with PDPN (defined as pain severity of ≥ 4 on 11-point numerical rating scale [NRS] measuring 24-hour pain scores [0 to 10] averaged over the last 7 days) who have not responded to at least two different classes of neuropathic pain medications as per NICE guidance.

The trial will have an internal pilot phase with stop/go criteria as described in section 8.1. The patients will be randomised in a 1:1 ratio to either FREMS + standard care or TENS + standard care. The primary outcome (24-hour pain NRS averaged over the last 7 days) is measured post-randomisation at 3 months and the final follow up is at 6 months post-randomisation. The administering team, the participant and the researchers will be blinded to treatment allocation.

Patients will be recruited from NHS Trusts that have PDPN services and the aligned primary care and podiatry services, as well as social media and Diabetes UK local patient groups. The study device delivering both FREMS and TENS will be placed in the Trusts at secondary care sites.

3.1 Safety and mechanistic sub-study

This sub-study is 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 sub-study will perform QST using the validated and standardised German Research Network on Neuropathic Pain (DFNS) protocol, which also has validated age and gender at birth normative values [67]. The DFNS has been shown to have good inter-observer and test-retest reliability for use in patients with sensory disturbances of different aetiologies to help identify mechanisms of neuropathic pain [68]. The DFNS protocol takes 60 minutes to perform and, in this trial, will only be conducted in two trial centres, Sheffield and Liverpool, as the Principal Investigators (PIs) in these centres have already been trained in the DFNS protocol. The DFNS will be performed at baseline, 3 months and 6 months. This sub-study will ensure the safety of FREMS treatment by examining any changes in QST (including sensory perception of sharp, cold, warm, or vibration stimuli) during the trial as performed in previous trials [69].

3.2 Assessment of risk

All clinical trials can be considered to involve an element of risk and in accordance with the Birmingham Clinical Trials Unit (BCTU) standard operating procedures this trial has been risk assessed to clarify any risks relating uniquely to this trial beyond that associated with usual care. A Risk Assessment has been conducted and concluded that this trial corresponds to the following categorisation: No higher than the risk of standard medical care.

4. ELIGIBILITY

4.1 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 one 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 [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 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.

4.2 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. Patient has a pacemaker, defibrillator or neurostimulator.
9. Pregnancy (see section 4.3)

4.3 Pregnancy

Pregnancy is an exclusion criterion as it is likely to confound various outcome measures used in FREMS-PDPN. However, there is no safety risk from either FREMS or TENS, and therefore pregnancy at baseline will be based on self-report, and there is no requirement for contraception throughout the trial. Pregnancy will be recorded at 3 and 6 month follow up visits.

4.4 Co-enrolment

Participants in FREMS-PDPN can participate in any observational study. Co-enrolment in other non-pain trials can be considered after discussion with members of the Trial Management Group (TMG).

5. CONSENT

5.1 Screening consent

It is the responsibility of the Principal Investigator (PI) to obtain written informed consent for each participant prior to any trial related procedures. The process for taking consent can be delegated to members of the local research team working on the trial at the site, all of whom should have undergone Good Clinical Practice (GCP) training. Delegation of this duty will be authorised by the PI and captured on the Site Delegation Log.

Where possible all eligible patients will be approached about the trial by their clinical care team members who will inform them of the study. Patients will be presented with a Participant Information Sheet (PIS) and a link to the trial online information tool which includes trial explanatory animations. At this visit (this can be done in clinic or remotely over the phone) the PI or delegate will provide further details of the study, i.e. adequately explain the aim of the trial, the trial interventions, and the anticipated benefits and potential hazards of taking part in the trial and will ensure that the potential participant has the opportunity to ask questions. The PI or delegate will again explain that participation is voluntary and that the participant is free to decide whether to take part in the trial, is not obliged to continue into the main trial, and may withdraw from the trial at any time. They will be given sufficient time to consider and, should the participant feel the need to do so, discuss participation with friends and family.

. Online consenting will be performed via a link generated by the REDcap database. This will be provided to all research sites at the start of the trial.

If a patient is identified at a PIC site, it will be the responsibility of that site to contact the recruiting centre to facilitate consent and trial entry. PIC sites will have access to the PIS and the patient information tool and are permitted to provide to patients prior to referring them to the research team.

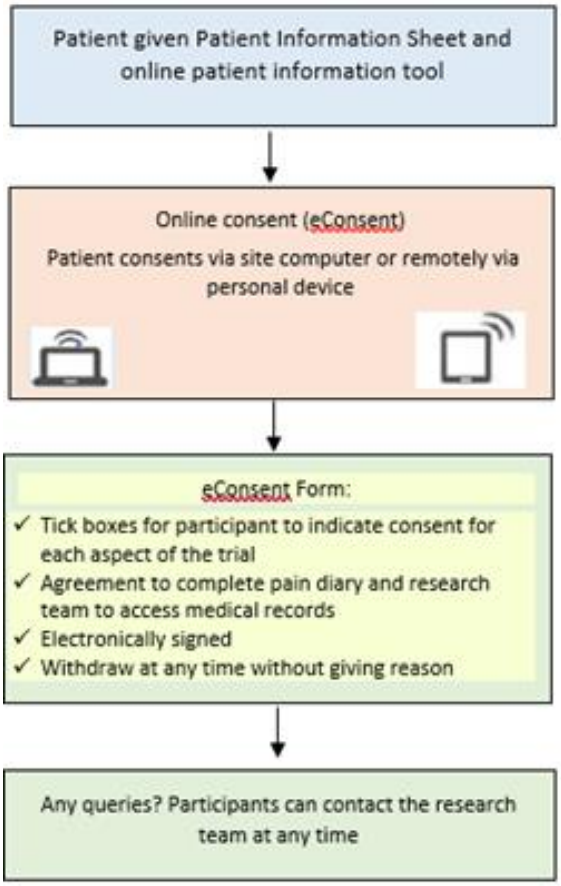
If potential participants are interested in taking part they will be asked to electronically sign and date the latest version of the electronic screening Informed Consent Form (ICF) which will be available to all sites online. This can be done at site via the site's computer/device or remotely via the patient's personal device. The PI or delegate(s) will then countersign and date the ICF. Should the consent be done remotely the site will receive an alert that the patient has consented and be able to access the consent form from the site's computer/device and countersign.

A printed copy of the ICF will be given to the participant. Should participants wish to do so, they can receive a copy of the signed ICF by consenting to provide an email address for the ICF to be emailed instead. A copy of the consent form will be placed in the medical notes. A copy will also be stored electronically in the site-specific section of the database. A copy will be printed for the Investigator Site File (ISF).

Details of the informed consent discussions will be recorded in the participant's medical notes. This will include date of discussion, the name of the trial, summary of discussion, version number of the PIS given to participant, version number of ICF signed and date consent received.

The participant will consent to allow the site team access to their medical notes to help confirm patient eligibility. The participant will also consent to the use of limited personal identifiable information such as name and telephone number in order for the site staff to register them into the screening phase of the trial. This will be done via the online system. Once the participant is registered they will receive a daily alert via text message to complete the pain dairy (starting the day after the participant is registered).

If the participant is later randomised into the trial, their trial number will be entered on the copy of the screening ICF maintained in the ISF and the TNO linked against the ICF stored in the database. At the time of screening consent, the participant will be asked to give explicit consent for the signed screening ICF to be stored in the database for internal review and audit purposes. If the participant does not enter the main trial, then the signed screening ICF and any personal identifiable information will be deleted 14 days after the date of the screening consent.



Consent to take part in screening for the trial will be completed online:

- This can be done at a time and location convenient to the participant, using a smartphone, computer or tablet, or at site.
- The eConsent form will consist of check boxes to indicate consent for each aspect of screening. Participants sign the eConsent form using a mouse or their finger.
- The participant must give explicit consent for the members of the site research team to be given direct access to the participant's medical records to assess eligibility.
- The participant must also consent to the collection of their pain scores for 7 days.
- Following the completion of the screening consent form, the trial database will contact the participant by text message to allow them to complete their electronic pain score diary.
- Participants will be emailed a copy of their consent form if they consent to the storage of their email address for this purpose (a printed copy will be provided if they do not).

5.2 Main Trial Consent

Once the participant has completed a week of daily pain scores (at least 5 out of 7 days must be completed to be considered a valid averaged score) the site will receive an alert via the online system informing them of the participant's average pain score. During completion of the daily pain scores, the site will confirm aspects of eligibility via the participant's medical notes as consented to in the screening ICF. If medical notes and pain score confirm eligibility the participant will be invited into clinic to complete any outstanding eligibility requirements.

At this visit the PI or delegate will reconfirm the participant is still willing to take part in the study.

If the participant confirms they are happy to enrol into the trial, they will be asked to consent to participate in the main trial and to randomisation (see section 6.4) by electronically signing and dating the latest version of the electronic main trial ICF. This will be done at site via the site's computer/device. The PI or delegate(s) will then countersign and date the ICF.

A printed copy of the ICF will be given to the participant. Should participants wish to do so, they can receive a copy of the signed ICF by consenting to provide an email address for the ICF to be emailed

instead. A copy will also be stored electronically in the site-specific section of the database. A copy will be printed for the Investigator Site File (ISF).

Details of the informed consent discussions will be recorded in the participant's medical notes. This will include date of discussion, the name of the trial, summary of discussion, version number of the PIS given to participant, version number of ICF signed and date consent received. A copy of the consent form will be placed in the medical notes. Where consent is obtained on the same day that trial related assessments start, a note should be made in the medical notes of the time the consent was obtained and what time the assessments started.

At each visit the participant's willingness to continue in the trial will be ascertained and documented in the medical notes. Throughout the trial the participant will have the opportunity to ask questions about it. Any new information that may be relevant to the participant's continued participation will be provided. Where new information becomes available which may affect the participants' decision to continue, participants will be given time to consider and if happy to continue will be re-consented. Re-consent will be documented in the medical notes. The participant's right to withdraw from the trial will remain.

5.3 Optional consent

Participants will be offered optional consent choices to allow linkage of their data available in NHS routine clinical datasets, including primary care data (e.g. Clinical Practice Research Datalink, The Health Improvement Network, QResearch) and secondary care data (Hospital Episode Statistics) through NHS Digital and other central UK NHS bodies. If participants agree, they will consent to the Trial Office sending their name, date of birth and NHS/CHI number to the relevant national registry and then for the national registry to link this to their data and send the information back to the Trial Office. The consent will also allow access to other new central UK NHS databases that will appear in the future. This will allow us (subject to receipt of additional funding via another grant application) to assess longer-term impact and health service usage data without needing further contact with the trial participants.

6. IDENTIFICATION, RANDOMISATION and BLINDING

6.1 Identification

Recruitment will take place from NHS Trusts with PDPN services and their aligned primary care and podiatry services. As this study requires a device that cannot be moved to where the patient is, the device will be placed centrally in the research centre and all patients whether recruited from primary or secondary care will receive the treatment in the research centre. A number of approaches will be taken to recruit participants:

1. Patients will be recruited from secondary care diabetes clinics, neuropathy clinics or pain clinics.
2. Working with the Clinical Research Network, patients will be recruited from primary care using GP registries. Identified GP practices will act as Participant Identification Centres (PICs) for the trial.
3. All currently planned centres have strong links with community podiatry services and this link will be used to identify appropriate patients. These services will act as PICs for the trial.
4. Once developed adverts will be put in outpatients in the NHS Trusts, primary care, and social media. As this material has not yet been developed it will be submitted as part of an amendment once the Regulatory approval have been obtained. Diabetes UK local patient groups will publicise the study. When social media is used, we will ensure that the information is clear that this is relevant to patients in certain locations.

NHS research staff may assist clinicians with caseload screening, use of electronic record searches or research registers/databases of existing patients (e.g. TriNetX) to help identify patients on their caseloads, according to local permissions as appropriate, for any of the methods described above.

All patients identified will receive a PIS and access to the online participant information tool. The online patient information tool has not yet been developed and will be submitted as an amendment once the Regulatory approval has been obtained. Patients will either give consent for the screening process at site or will receive a link to the screening consent to collect the pain scores over 7 days and access the participant's medical notes to assess study eligibility (see section 5.1). This will contain details of the study team to contact for further information. Advertising materials, once developed, will also contain contact details for further information.

The study team will endeavour to recruit patients from a diverse population based on gender at birth, social deprivation and ethnicity. This should be possible considering that PDPN is strongly associated with socioeconomic disadvantage and is more common in South Asians compared to White Europeans [71, 72]. Some of the trial centres are well experienced in recruiting patients from ethnic minorities, such as Kings College Hospital which has a large Afro-Caribbean population in the foot clinic and Birmingham which has a large South Asian population in the neuropathy and foot clinics. We will also approach the South Asian Health Foundation to publicise the study. Recruitment from primary care and working with the local patient groups will also allow us access to a larger more diverse population than relying on recruitment from secondary care only. We will monitor recruitment and adapt strategies accordingly if needed.

6.2 Participant Identification Centres

At some sites, participants will be recruited via participant identification centres (PICs) and referred to the main randomising centre.

6.3 Screening

Screening of potential participants will be conducted by the clinical team and/or the local research team as indicated above.

Anonymised details of all participants approached about the trial will be recorded on the FREMS Participant Screening Log which will be kept in the ISF, and should be available to be sent to the Trial Office upon request.

6.4 Randomisation

After consent has been obtained and full eligibility confirmed by a medically qualified doctor (as per section 5.2) the full baseline battery of questionnaires and Case Report Forms (CRFs) will be completed and the participant will be randomised into the trial.

Randomisation will be provided by BCTU using a secure online system (available at www.fremspdpn.bctu.bham.ac.uk), thereby ensuring allocation concealment. Unique log-in usernames and passwords will be provided to those who have been delegated the role of randomising participants into the trial as detailed on the FREMS-PDPN Site Delegation Log. These unique log-in details must not be shared with other staff and in no circumstances should staff at sites access the system using another person's login details. The online system will be available 24 hours a day, 7 days a week, apart from short periods of scheduled maintenance.

6.4.1 Randomisation process

Randomisation Forms will be provided to investigators and may be used to collate the necessary information prior to randomisation. All questions and data items on the online Randomisation Form must be answered prior to a potential participant being randomised and a Trial Number being issued.

Following randomisation, a confirmatory e-mail will be sent to the randomiser and PI.

The local research team should add the participant to the FREMS-PDPN Participant Recruitment and Identification Log which links participants with their Trial Number. Sites must maintain this document securely and it must not be submitted to the Trial Office. The FREMS-PDPN Participant Recruitment and Identification Log should be held in strict confidence.

6.4.2 Randomisation method

Participants will be randomised at the level of the individual in a 1:1 ratio to either FREMS or TENS via a secure web-based system at BCTU. The randomisation will use a minimisation algorithm to ensure balance in the treatment allocation taking into account centre, age (18-39, 40-59, 60+), gender at birth, diabetes type, ethnicity (White, Asian/Asian British, Black/African/Caribbean/Black British, Other ethnic group) and opioid use (yes/no). To avoid the possibility of the intervention allocation becoming predictable, a random element will be included in the algorithm. Full details of the randomisation specification will be stored in a confidential document at BCTU.

6.5 Blinding

The FREMS device used in this study will deliver both FREMS and TENS interventions. It is operated by inserting a numbered key card pre-programmed by the supplier with the randomised allocation. At randomisation each participant will be allocated a unique key card number by the randomisation database to be used only for that participant. The administering team will follow the same procedure for all participants administering the intervention in terms of electrodes positioning and setting the electrical dose. Patients will be instructed not to consider any perception at the site of electrode placement during the treatment as a sign of active treatment and also not to judge the absence of any such perception as a sign of sham treatment, similar to previous RCTs [43, 44] as current perception varies according to the severity of the neuropathy and the site of the electrode [73, 74]. Using TENS will allow patients who still have remaining sensation to feel the “buzzing” which is also felt by delivering FREMS. These measures will ensure blinding of the delivery team, investigators and participants as both treatments will be delivered in the same way via the same machine and participants will feel electrical buzzing in both treatments.

6.5.1 Blinded personnel

Trial participants, the site study teams, the CI, co-investigators, the study statisticians and Trial Office will all be blinded to the trial interventions.

6.6 Unblinding

Unblinding will not be available during the trial. FREMS and TENS are both neuromodulation treatments working via stimulation of superficial nerve fibres. 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. Unblinding would not contribute anything to the clinical management of the patient in any clinical situation.

6.7 Informing the participant's GP and other parties

If the participant has agreed, the participant's GP should be notified that they are in the FREMS-PDPN trial, using the FREMS-PDPN GP Letter.

7. TRIAL INTERVENTION

7.1 Trial intervention and dosing schedule

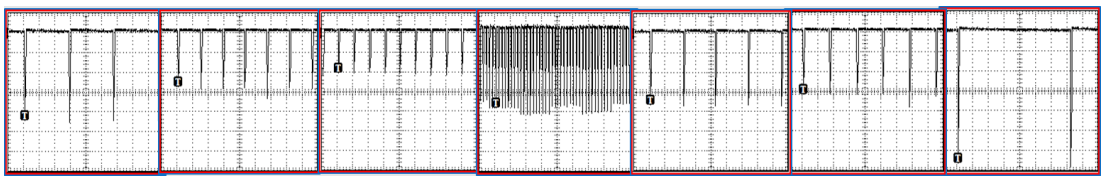
FREMS is a non-invasive treatment modality for several chronic painful conditions. The device consists of the FREMS unit (**Figure 1**) including a liquid crystal display with touchscreen, 1 power supply unit and power cable, 1 remote control, electrode connection cables for neuromodulation, electrodes, 1 user treatment key card and 1 connection protection cover.

Figure 1: APTIVA FREMS equipment and electrodes positions

During a treatment session, a series of biphasic asymmetric electric sequences of negative pulses with double modulation (frequency and duration) are delivered through disposable electrode pads applied to the skin along the pathway of the nerve involved in the neuropathy. The pulses (**Figure 2**) are characterised by:

- sharp spike and an asymmetrical shape with a peak amplitude variable from 0 V to 255 V
- pulse frequency variable within the range of 0 Hz to 50 Hz
- pulse duration variable within the range of 10 µs to 40 µs

Figure 2: An example of FREMS pulse sequence



For PDPN, 8 electrode pads (2 per connection cable) are applied to the calf, shinbone, ankle and midfoot of each leg. At the beginning of each treatment session, the electrical dose is set by the healthcare professional, based on the sensation felt by the patient: the electrical stimulation should be felt but should not be painful. Hence the current is increased gradually till the patient feels it without discomfort and the strength of the current is set at that point. This process is repeated for each individual electrode position separately. The duration of a treatment session is 35 minutes with a treatment cycle comprising 10 daily sessions (two working weeks) as per manufacturer instructions and the previous clinical trials that used FREMS. The device is CE marked and training, including a detailed manual and training video, will be provided prior to the site opening to recruitment. Each site will also be visited by an investigator during the first six months of recruitment at their site to quality check the use of the FREMS machine.

Participants will be randomised to receive:

- FREMS during 10, 35-minute sessions over 10 working days (in addition to standard care).

OR

- TENS during 10, 35-minute sessions over 10 working days (in addition to standard care).

It is expected that treatment will start on the same day as randomisation; if not, treatment must start within 7 days.

7.2 Interactions or contraindications

7.2.1 Concomitant medication(s)/intervention(s)

Regular pain medication should continue as per routine care during trial participation.

7.2.2 Prohibited medication(s)/intervention(s)

There are no prohibited medications or interventions in FREMS-PDPN.

7.3 Intervention modification or discontinuation

In case of painful side effects from the treatment the amplitude of stimulation may be lowered; in case of intolerable side effects the stimulation will be stopped and the participant withdrawn from further treatment. A description of the perceived intolerable sensation will be recorded.

7.4 Intervention supply and storage

The CE marked FREMS/TENS device will be supplied by BHR Pharmaceuticals Ltd, 41 Centenary Business Centre, Hammond Close, Nuneaton, Warwickshire, CV11 6RY. It should be stored in a secure room at each site but otherwise has no specific storage requirements. The device will be supplied with consumables and will be returned to BHR Pharmaceuticals at the end of the trial.

7.5 Adherence

Adherence to treatment will be recorded as the number of completed treatment sessions (i.e. all 35 minutes) for every participant. Participants will be considered as adherent when they attend 4 or more out of 5 sessions for each week of treatment.

7.6 Post-trial care

There is no provision for post-trial care. The FREMS machine is not yet generally available in the NHS outside of this trial.

8. OUTCOME MEASURES

8.1 Internal pilot outcomes

1. To assess the feasibility of identifying eligible patients.
2. To assess the acceptability of randomisation to receive the intervention or not.
3. To determine if the pilot phase should continue to a full trial.

The stop/go criteria will be assessed after 6 months of recruitment. The internal pilot's primary criteria will assess recruitment per centre per month. The target recruitment for each site will be 2 participants per month. With staggered opening of sites (2 sites per month), it is anticipated that at 6 months, 22% of the total recruitment target will have been met. Therefore, the internal pilot recruitment target is 80 participants.

We will apply a traffic light system as described below:

- Green: ≥100% of mean target recruitment per centre per month: progress to full trial.
- Amber: 60%-99% of target recruitment per centre per month: discuss feasibility with the Trial Steering Committee (TSC) and develop improvement plans. Aspects evaluated to guide improving recruitment will include: number of eligible patients identified, percentage of patients randomised and reasons for non-randomisation, recruitment site performance, and review of recruitment procedures.
- Red: <60% of the target recruitment per centre per month: Discuss cessation of the trial with the TSC and the trial funder, the National Institute for Health Research (NIHR).

Note: In light of the ongoing uncertainties during the COVID-19 pandemic and ongoing disruption to health and Research and Development Services, additional actions (e.g. increasing number of sites opened) to support recruitment may be necessary to achieve the pilot targets in an appropriate timeframe.

Table 4: Internal pilot progression criteria

Internal pilot recruitment target = 80 participants by 6 months			
	Red	**Amber**	**Green**
Participants recruited per centre per month	<1.2	1.2-1.9	≥2
% of target recruitment per centre per month	<60%	60%-99%	≥100%
Number of centres opened (NB: out of 10)	<6	6-7	≥8

We will also consider the following throughout the internal pilot to determine if changes to trial processes are required: adherence (as a percentage of treatment sessions completed), and proportion of potentially eligible patients screened.

8.2 Main trial outcomes

All the outcomes listed in this section are in line with IMMPACT consensus recommendations for interpreting the clinical importance of treatment outcomes in clinical trials of the efficacy and effectiveness of chronic pain treatments [45]. IMMPACT highlights 4 core domains:

1. Pain intensity, assessed by a 0 to 10 NRS
2. Physical functioning
3. Emotional functioning
4. Participant ratings of overall improvement, assessed by the PGIC and Clinician Global Impression of Change (CGIC) with a 7 point Likert scale.

8.3 Primary outcome

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.

8.4 Secondary outcomes

8.4.1 Clinical

1. 7-day average 24-hour pain on an 11-point NRS scale (0 = no pain and 10 = worst pain imaginable) measured at the end of treatment) and at 6 months.
2. Neuropathic Pain Impact on Quality-of-Life Questionnaire (NePIQoL) as a measure of disease specific quality of life 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. Brief Pain Inventory-Diabetic Peripheral Neuropathy (BPI-DPN) as a measure of pain interference with function total score at 3 and 6 months.
7. Beck Depression Inventory as a measure of depression at 3 and 6 months.
8. Pittsburgh Sleep Quality Index (PSQI) as a general measure of sleep quality at 3 and 6 months.
9. Patient and Clinician Global Impression of Change at end of treatment, 3 months and 6 months.
10. Changes to pain medications (frequencies and dosages) at 3 and 6 months.
11. Patient perception of their treatment arm at the end of the treatment phase.

8.4.1 Cost-Effectiveness

1. Health-related QoL at 6 months assessed by the EuroQoL-5D-5L.
2. Health resource use at 3 and 6 months.
3. Cost per quality adjusted life year (QALY) gained over 6 months.

8.4.2 Safety

3. Frequency and proportion of Adverse Events.
4. Frequency of Serious Adverse Events.

8.4.3 Subgroup outcomes

The NPSI questionnaire will be used for subgroup analysis relating pain phenotype to treatment response [75]. There is emerging evidence that treatment response may be determined by a patient's pain phenotype [76-78]. In particular, these outcomes will be evaluated:

1. "Burning (superficial) spontaneous pain" NPSI mean subscores at end of treatment, 3 months and 6 months.
2. "Pressing (deep) spontaneous pain" NPSI mean subscores at end of treatment, 3 months and 6 months.
3. "Paroxysmal pain" NPSI mean subscores at end of treatment, 3 months and 6 months.
4. "Evoked pain" NPSI mean subscores at end of treatment, 3 months and 6 months.
5. "Paresthesia/dysesthesia" NPSI mean subscores at end of treatment, 3 months and 6 months.
6. NPSI mean total score at end of treatment, 3 months and 6 months.

8.5 Safety sub study

This sub study is aimed at ensuring that there is no worsening sensory dysfunction with the trial interventions. This sub study will perform QST using the validated and standardised DFNS protocol, which has validated age and gender at birth normative values [67]. The DFNS has been shown to have good inter-observer and test-retest reliability for use in patients with sensory disturbances of different aetiologies to help identify mechanisms of neuropathic pain [68]. The DFNS protocol takes 60 minutes to perform and will only be conducted in two trial centres, Sheffield and Liverpool, as the PIs in these

centres have been trained in the use of the DFNS. The DFNS will be performed at baseline and 3 months. This sub study will ensure the safety of FREMS treatment by examining for any changes in QST (including sensory perception of sharp, cold, warm, or vibration stimuli) during the trial as performed in previous trials [69].

9. TRIAL PROCEDURES

The intervention (FREMS or TENS) will be delivered by a research nurse or a health care assistant.

For trial assessments please see Table 5. The trial visits and data collected are summarised below:

Visit -1: Remote screening consent for potentially eligible patients followed by 1 week of daily NRS to assess eligibility based on a mean pain severity score of 4 and above. The daily NRS will be collected via text message or email during this period and throughout trial follow up if the participant is subsequently randomised into the trial.

Visit 0: Trial eligibility and consent, randomisation and collection of baseline data. All the data required to assess eligibility will be collected. In addition, other essential data for the trial will be collected including age, ethnicity, gender at birth, diabetes type, diabetes duration, medications history, past medical history, smoking history, alcohol intake, blood pressure, weight, height.

Visit 1-10: 10 FREMS or TENS sessions over 2 weeks, 35 minutes each. For data collected at visit 10 (End of treatment), please see Table 5.

Visits 11-12: At 3 and 6 months respectively. For assessments please see Table 5.

Long-term follow up: Participant consent will be sought to access routinely collected NHS data to assess health resource usage beyond the end of this trial as per section 4.3.

NB: it is expected that in most cases Visits 0 and 1 will be combined in order to start treatment on the day of randomisation.

9.1 Schedule of assessments

Table 5: Schedule of Assessments

Assessment	Screening (visit -1)	Baseline (visit 0)	End of treatment (visit 10)	3 months post-randomisation (visit 11)	6 months post-randomisation (visit 12)
Informed consent	X	X			
Eligibility checked	X	X			
NRS*	X	X	X	X	X
MNSI		X			X**
DN-4		X			
NPSI		X	X	X	X
Medications		X		X	X
Patient GIC			X	X	X
Clinician GIC			X	X	X
Beck Depression Inventory		X		X	X
EQ5D-5L		X		X	X
NePIQoL		X		X	X
PSQI		X		X	X
BPI-DPN		X		X	X
HbA1c if not done in the last 2 months		X			
Medical history and examination		X			X
Health resource usage				X	X
DFNS quantitative sensory testing**		X		X	X
AE review			X	X	X

NRS: collected daily via text messages or emails and the average of the last 7 days will be calculated at each time point.*

***: These will be performed to ensure no worsening neuropathy in selected centres only.*

9.2 Withdrawal and changes in levels of participation

Informed consent is defined as the process of learning the key facts about a clinical trial before deciding whether or not to participate. It is a continuous and dynamic process and participants should be asked about their ongoing willingness to continue participation at all visits. Participants should be aware from the beginning that they can freely withdraw (cease to participate) from the trial at any time. A participant may wish to cease to participate in a *particular* aspect of the trial.

Participants found to be ineligible post-randomisation should be followed up according to all trial processes and will still have their data analysed unless they explicitly change their level of participation.

The changes in levels of participation within the trial are categorised in the following ways:

No trial intervention: The participant would no longer like to receive the trial intervention but is willing to be followed up in accordance with the schedule of assessments and if applicable using any central UK NHS bodies for long-term outcomes (i.e. the participant has agreed that data can be collected and used in the trial analysis).

No trial related follow-up: The participant does not wish to attend trial visits in accordance with the schedule of assessments but is willing to be followed up at standard clinic visits and if applicable using any central UK NHS bodies for long-term outcomes (i.e. the participant has agreed that data can be collected at standard clinic visits and used in the trial analysis, including data collected as part of long-term outcomes).

No further data collection: The participant is not willing to be followed up in any way for the purposes of the trial AND does not wish for any further data to be collected (i.e. only data collected prior to any changes of levels in participation can be used in the trial analysis).

The details of changes of levels in participation within trial (date, reason and category of status change) should be clearly documented in the source documents.

10.ADVERSE EVENTS REPORTING

10.1 Definitions

Table 6: Adverse event reporting definitions

Severity Definitions	Mild	Awareness of signs or symptoms that do not interfere with the participant's usual activity or are transient and resolved without treatment and with no sequelae.
	Moderate	A sign or symptom, which interferes with the participant's usual activity.
	Severe	Incapacity with inability to do work or perform usual activities.
Adverse Event	AE	Any untoward medical occurrence in a participant participating in the trial which does not necessarily have a causal relationship with the intervention received.
Related Event	RE	An event which resulted from the administration of any of the research procedures.
Serious Adverse Event	SAE	An untoward occurrence that: Results in death Is life-threatening* Requires hospitalisation or prolongation of existing hospitalisation Results in persistent or significant disability or incapacity Consists of a congenital anomaly/ birth defect

		Or is otherwise considered medically significant by the Investigator**
Unexpected Event	UE	The type of event that is not listed in the protocol as an expected occurrence.
Related and Unexpected Serious Adverse Event	N/A	A SAE that meets both the definition of a Related and Unexpected Event.

** The term life-threatening is defined as diseases or conditions where the likelihood of death is high unless the course of the disease is interrupted.*

*** Medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the participant or may require intervention to prevent one of the other outcomes listed in the definitions above.*

10.2 Adverse event recording – general

The recording and reporting of Adverse Events (AEs) will be in accordance with the UK Policy Framework for Health and Social Care Research, the Principles of GCP as set out in the UK Statutory Instrument (2004/1031; and subsequent amendments) and the requirements of the Health Research Authority (HRA). Definitions for adverse event reporting are listed in **Table** 6: Adverse event reporting definitions in Section 10.1.

It is routine practice to record AEs in the participant's medical notes and it is also recommended that this includes the documentation of the assessment of severity and seriousness and also of causality (relatedness) in relation to the intervention(s) in accordance with the protocol.

10.3 AE reporting in FREMS-PDPN

The reporting period for AEs in FREMS-PDPN will be from the start of treatment until the end of trial follow-up.

The safety profile for this trial population and interventions are well characterised so a strategy of targeted reporting of AEs will not affect the safety of participants. Only those AEs detailed below will be reported:

- Serious Adverse Events (SAEs) (reported on trial specific SAE CRF).
- AEs possibly or definitely related to trial treatment, occurring between the start of trial treatment and 7 days after the end of the trial treatment period (reported on trial specific AE log).

10.4 SAE reporting in FREMS-PDPN

For all SAEs, the PI or delegate must do one of the following:

1. **Record safety reporting-exempt SAEs** in the medical notes but **not report** them to the Trial Office on an SAE form as per Section 10.4.1.

2. **Report SAEs to the trial office in a non-expedited manner**. This can only be done for the pre-defined subset of SAEs as per Section 10.4.2.

3. **Report SAEs to the trial office in an expedited manner**. All SAEs not covered by the above 2 categories must be reported within 24 hours of the site research team becoming aware of the event.

Note: when an SAE occurs at the same hospital at which the participant is receiving trial intervention or is being followed up for trial purposes, processes must be in place to make the trial team at the hospital aware of any SAEs, regardless of which department first becomes aware of the event, in an expedited manner.

10.4.1 SAEs not requiring reporting to the Trial Office

At whatever time they occur during an individual's participation, during the AE reporting period, the following are not considered to be critical to evaluations of the safety of the trial:

- Pre-planned hospitalisation
- Hospital admissions lasting less than 24 hours

All events which meet the definition of serious must be recorded in the participant notes, including the causality and severity, throughout the participant's time on trial, including follow-up, but for trial purposes these events do not require reporting on the SAE Form. Such events are "safety reporting exempt".

10.4.2 SAEs requiring non-expedited reporting to the Trial Office

Where the safety profile is well established, the causal relationship between the intervention (or the participant's underlying condition) and the SAE may be known. That is, such events are protocol-defined as "expected" (see Section 10.7 Assessment of expectedness of an SAE by the CI).

Such events should still be recorded by the trial team in the participant's notes and reported to the Trial Office on the trial specific SAE form but do not require expedited reporting (immediately on the site becoming aware of the event) since the assessment of expectedness for the specified events has been pre-defined. It is expected that these SAEs are reported within 7 days of the site becoming aware of the event. These include:

- Hospitalisations related to DM or other pre-existing conditions

10.4.3 SAEs requiring expedited reporting to the Trial Office

All SAEs not listed in Sections 0 and 10.4.2 must be reported to the Trial Office on the trial specific SAE form within 24 hours of the site research team becoming aware of the event.

10.5 SAE Reporting process

On becoming aware that a participant has experienced an SAE which requires reporting on an SAE form, the PI or delegate should report the SAE to their own Trust in accordance with local practice and to the Trial Office.

To report an SAE to the Trial Office, the PI or delegate must complete, date and sign the trial specific SAE form. The completed form together with any other relevant, appropriately anonymised, data should be submitted to the Trial Office using the information below in accordance with the timelines given in Section 10.4.2 and 10.4.3.

To report an SAE, submit the SAE Form to:

www.fremspdpn.bctu.bham.ac.uk

Where an SAE Form has been completed by someone other than the PI initially, the original SAE form must be countersigned by the PI to confirm agreement with the causality and severity assessments.

On receipt of an SAE form, the Trial Office will allocate each SAE a unique reference number and notify the site via email to the site as proof of receipt. The site and the Trial Office should ensure that the SAE reference number is quoted on all correspondence and follow-up reports regarding the SAE and filed with the SAE in the ISF.

If the site has not received confirmation of receipt of the SAE or if the SAE has not been assigned a unique SAE identification number within 1 working day of reporting, the site should contact the Trial Office.

10.6 Assessment of causality of an SAE

When completing the SAE form, the PI (or, throughout this section, a medically qualified delegate) will be asked to define the nature of the seriousness and causality (relatedness; see Table 7: Categories of causality) of the event.

In defining the causality the PI must consider if any concomitant events or medications may have contributed to the event and, where this is so, these events or medications should be reported on the SAE form. It is not necessary to report concomitant events or medications which did not contribute to the event.

As per **Table 7**, all events considered to be 'possibly', 'probably', or 'definitely' related to the intervention will be reported by the Trial Office as 'related'; all events considered at site to be 'unlikely' or 'unrelated' to the intervention will be reported by the Trial Office as 'unrelated'. The same categorisation should be used when describing AEs and protocol-exempt SAEs in the source data.

Table 7: Categories of causality

Category	Definition	Causality
Definitely	There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.	Related
Probably	There is evidence to suggest a causal relationship, and the influence of other factors is unlikely.	
Possibly	There is some evidence to suggest a causal relationship. However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant events or medication)	
Unlikely	There is little evidence to suggest there is a causal relationship. There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant events or medication).	Unrelated
Not related	There is no evidence of any causal relationship.	

On receipt of an SAE Form, the Trial Office will forward it, with the unique reference number, to the Chief Investigator (CI) or delegate who will independently* review the causality of the SAE. An SAE judged by the PI or CI or delegate to have a reasonable causal relationship ("Related" as per **Table** 7: Categories of causality) with the intervention will be regarded as a related SAE. The severity and causality assessment given by the PI will not be downgraded by the CI or delegate. If the CI or delegate disagrees with the PI's causality assessment, the opinion of both parties will be documented, and where the event requires further reporting, the opinion will be provided with the report.

*Where the CI is also the reporting PI an independent clinical causality review will be performed.

10.7 Assessment of expectedness of an SAE by the CI

The CI or delegate will assess related SAEs for expectedness with reference to the criteria in **Table 8**.

Table 8: Categories of expectedness

Category	Definition
Expected	An adverse event that is consistent with known information about the trial related procedures, trial intervention (as described in the manufacturer's guidance) or pre-existing conditions of the participant (including DM).
Unexpected	An adverse event that is not consistent with known information about the trial related procedures, trial intervention, or pre-existing conditions of the participant.

If the event is unexpected (i.e. it is not defined in the protocol as an expected event) it will be classified as a related and unexpected SAE.

The CI will undertake review of all SAEs and may request further information from the clinical team at site for any given event to assist in this.

10.8 Provision of SAE follow-up information

Following reporting of an SAE for a participant, the participant should be followed up until resolution or stabilisation of the event. Follow-up information should be provided using the SAE reference number provided by the Trial Office. Once the SAE has been resolved, all critical follow-up information has been received and the paperwork is complete, a copy of the final version of the completed SAE form must be submitted to the Trial Office and a copy printed to be stored in the ISF.

10.9 Reporting SAEs to third parties

The independent Data Monitoring Committee (DMC) may review any SAEs at their meetings.

The Trial Office will submit a progress report to the Research Ethics Committee (REC) and University of Birmingham (UoB) Research Governance Team (RGT) annually starting 12 months after the date of the favourable opinion was given. An electronic copy should be emailed to the REC within 30 days of the end of the reporting period.

The Trial Office will report all events categorised as Unexpected and Related SAEs to the REC and RGT within 15 days of being notified.

Details of all Unexpected and Related SAEs and any other safety issue which arises during the course of the trial will be reported to the PIs. A copy of any such correspondence should be filed in the ISF and Trial Master File (TMF).

11.DATA HANDLING AND RECORD KEEPING

11.1 Source data

Source data is defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. In order to allow for the accurate reconstruction of the trial and clinical management of participants, source data will be accessible and maintained.

In FREMS-PDPN, some data variables may be entered directly onto the CRF; these are clearly identified and detailed in **Table** 9: Source data in FREMS-PDPN.

Table 9: Source data in FREMS-PDPN

Data	**Source**
Participant Reported Outcomes	The original completed eCRF on the BCTU database is the source and will be held on BCTU servers. If the participant completes paper forms, the original paper copies are the source data and sites will upload this data to the trial database.
Pain Numerical Rating Scale	The participant's responses as received directly by the eCRF by text or email are the source data, and will be held on BCTU servers.
Baseline, end of treatment and 3/6 month CRFs	Data is entered directly onto the eCRF which is the source. It is held on BCTU servers.
Clinical event data	The original clinical annotation is the source document. This may be found on clinical correspondence, or electronic or paper participant records. Clinical events reported by the participant, either in or out of clinic (e.g. phone calls), must be documented in the source documents.
Recruitment	The randomisation eCRF is the source. It is held on BCTU servers.
Change of status	The change of status form is the source data and will be held on BCTU servers. This form will be completed by site research staff directly onto the eCRF.

11.2 Case Report Form (CRF) completion

The CRFs will include (but will NOT be limited to) the following Forms (see **Table 10**).

Table 10: Case report forms in FREMS-PDPN

Form Name	**Schedule for submission**
Consent Form	At the point of completing eligibility screening
Pain diary	Automatic submission upon completion – should be completed daily
Informed Consent Form	At the point of consent
Participant Contact Details Form	At the point of consent
Baseline CRF	As soon as possible after consent
Randomisation CRF	At the point of randomisation
End of treatment CRF	As close to the end of treatment date as possible
3-month CRF	As close to the 3 month follow up time point as possible
6-month CRF	As close to the 6 month follow up time point as possible
Change of Status Form	At the point of change of status, withdrawal or death
SAE reporting Form	At the point of being aware of an SAE

A CRF should be completed for each individual participant. Data should be submitted in a timely manner i.e. within four weeks of submission schedule.

In all cases it remains the responsibility of the PI to ensure that the CRF has been completed correctly and that the data are accurate. This will be evidenced by the electronic sign off of the PI or delegate. The Site Delegation Log will identify all those personnel with responsibilities for data collection.

The delegated staff completing the CRF should ensure the accuracy, completeness and timeliness of the data reported. This will be evidenced by the electronic sign off of the CRF.

Data reported on each CRF will be consistent with the source data and any discrepancies will be explained. All missing and ambiguous data will be queried. Staff delegated to complete CRFs will be trained to adhere to FREMS-PDPN CRF completion guidelines.

The following guidance applies to data and partial data:

- Time format – all times should be in accordance with the 24hr clock.
- Rounding conventions – rounding should be to the nearest whole number: If the number you are rounding is followed by 5, 6, 7, 8, or 9, round the number up. **Example**: 3.8 rounded to the nearest whole number is 4. If the number you are rounding is followed by 1, 2, 3 or 4, round the number down. **Example**: 3.4 rounded to the nearest whole number is 3.
- Trial-specific interpretation of data fields – where guidance is needed additional information will be supplied.
- Entry requirements for concomitant medications (generic or brand names) – generic names should be used where possible.
- Missing/incomplete data – should be clearly indicated – all blank fields will be queried by the Trial Office.
- Protocol and GCP non-compliances should be reported to the Trial Office on discovery.

11.3 Participant completed questionnaires

The NRS pain diary will be completed daily, with text reminders (or optional emails) sent to complete by return text.

Other participant completed questionnaires can be completed on paper in clinic (to be entered by site staff) or online as per participant preference. If completed in clinic, the participant will complete under the supervision of a local researcher, who should ensure completeness. If completed remotely, a reminder and link will be sent to the participant at the due date by text or email as per participant preference. If not completed within 7 days, an additional reminder will be sent.

Questions relating to suicidal thoughts are asked in some of the participant completed questionnaires. Should the patient answer yes to these there will be a pre-programmed trigger built into the ReDCAP system alerting sites that the patient has flagged as a risk. It will be the sites responsibility to act accordingly and follow this up with the patient in line with their local policy.

11.4 Data management

Processes will be employed to facilitate the accuracy and completeness of the data included in the final report. These processes will be detailed in the trial specific Data Management Plan and include the processes of data entry and data queries.

Data entry will be completed by the sites via a bespoke BCTU ReDCAP trial database. The data capture system will conduct automatic range checks for specific data values to ensure high levels of data quality. Queries will be raised using data clarification forms (DCFs) via the trial database, with the expectation that these queries will be completed by the site within 30 days of receipt. Overdue data entry and data queries will be requested on a monthly basis.

11.5 Self-evident corrections

No self-evident corrections will be permitted in FREMS-PDPN.

11.6 Data security

UoB has policies in place which are designed to protect the security, accuracy, integrity and confidentiality of Personal Data. The trial will be registered with the Data Protection Officer at UoB and will hold data in accordance with the Data Protection Act (2018 and subsequent amendments). The Trial Office has arrangements in place for the secure storage and processing of the trial data which comply with UoB policies.

The Trial Database System incorporates the following security countermeasures:

Physical security measures: restricted access to the building, supervised onsite repairs and storages of back-up tapes/disks are stored in a fire-proof safe.

Logical measures for access control and privilege management: including restricted accessibility, access-controlled servers, separate controls of non-identifiable data.

Network security measures: including site firewalls, antivirus software and separate secure network protected hosting.

System management: the system will be developed by the Programming Team at the Trial Office and will be implemented and maintained by the Programming Team.

System design: the system will comprise of a database and a data entry application with firewalls, restricted access, encryption and role-based security controls.

Operational processes: the data will be processed and stored within BCTU.

System audit: The system will benefit from the following internal/external audit arrangements:

- Internal audit of the system
- Periodic IT risk assessment

Data Protection Registration: UoB's Data Protection Registration number is Z6195856.

11.7 Archiving

It is the responsibility of the PI to ensure all essential trial documentation and source documents (e.g. signed ICFs, Investigator Site Files, participants' hospital notes, copies of paper CRFs) at their site are securely retained for the contractual period (at least 10 years). Archiving will be authorised by BCTU on behalf of UoB following submission of the end of trial report. No documents should be destroyed without prior approval from the BCTU Director or their delegate.

The TMF will be stored at BCTU for at least 3 years after the end of the trial. Long-term offsite data archiving facilities will be considered for storage after this time; data will be stored securely and confidentially for at least 10 years. BCTU has standard processes for both hard copy and computer database legacy archiving.

12.QUALITY CONTROL AND QUALITY ASSURANCE

12.1 Site set-up and initiation

All PIs will be asked to sign the necessary agreements including a Site Delegation log between the PI and the Trial Office, a site agreement between site and Sponsor, and supply a current CV and GCP certificate. All members of the site research team are required to sign the Site Delegation Log, which details which tasks have been delegated to them by the PI. The Site Delegation Log should be kept up to date by the PI. It is the PI's responsibility to inform the Trial Office of any changes in the site research team.

Prior to commencing recruitment, each recruiting site will undergo a process of site initiation, either a meeting or a videoconference, which key members of the site research team are required to attend, covering aspects of the trial design, protocol procedures, AE reporting, collection and reporting of data and record keeping. Sites will be provided with an ISF containing essential documentation, instructions, and other documentation required for the conduct of the trial.

12.2 Monitoring

The central and on-site monitoring requirements for this trial have been developed in conjunction with the trial specific risk assessment and are documented in the trial specific monitoring plan.

12.3 On-site monitoring

For this trial, all sites will be monitored in accordance with the trial risk assessment and monitoring plan. Any monitoring activities will be reported to the Trial Office and any issues noted will be followed up to resolution. Additional on-site monitoring visits may be triggered. PIs and site research teams will allow the FREMS-PDPN trial staff access to source documents as requested. The monitoring will be conducted by BCTU/UoB staff.

12.4 Central monitoring

The Trial Office will check received ICFs and CRFs for compliance with the protocol, data consistency, missing data and timing at a frequency and intensity determined by the Data Management Plan. Sites will be sent DCFs requesting missing data or clarification of inconsistencies or discrepancies.

12.5 Audit and inspection

The Investigator will permit trial-related monitoring, audits, ethical review, and regulatory inspections at their site and provide direct access to source data/documents. This will be done both on site and remotely. The investigator will comply with these visits and any required follow-up. Sites are also requested to notify the Trial Office of any relevant inspections or local audits.

12.6 Notification of Serious Breaches

The sponsor is responsible for notifying the REC of any serious breach of the conditions and principles of GCP in connection with that trial or of the protocol relating to that trial. Sites are therefore requested to notify the Trial Office of any suspected trial-related serious breach of GCP and/or the trial protocol as soon as they become aware of them. Where the Trial Office is investigating whether or not a serious breach has occurred, sites are also requested to co-operate with the Trial Office in providing sufficient information to report the breach to the REC where required and in undertaking any corrective and/or preventive action.

Sites may be suspended from further recruitment in the event of serious and persistent non-compliance with the protocol and/or GCP, and/or poor recruitment.

13. END OF TRIAL DEFINITION

The end of trial will be the date of the last data capture including confirmation of resolution of all DCFs. This will allow sufficient time for the completion of protocol procedures, data collection and input and data cleaning. The Trial Office will notify the REC and the Sponsor within 90 days of the end of trial. Where the trial has terminated early, the Trial Office will notify the REC and the sponsor within 15 days of the end of trial. The Trial Office will provide the REC and the Sponsor with a summary of the clinical trial report within 12 months of the end of trial.

14. STATISTICAL CONSIDERATIONS

14.1 Sample size

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 [79]. The minimum clinically relevant improvement is pain severity in pain trials is determined as 2 points on the NRS (equivalent to 30% reduction in pain) [45, 80].

To detect a mean difference of 0.6 points between groups at 3 months using the standard method of difference between means using 2-sided t-test and assuming a standard deviation of 1.65 [81] (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) [82].

14.2 Analysis of outcomes

A separate Statistical Analysis Plan will be produced and will provide a more comprehensive description of the planned statistical analyses. A brief outline of the planned analyses is given below.

The primary comparison groups will be composed of those randomised to FREMS and standard care versus those randomised to TENS and standard care. In the first instance, all analyses will be based on the intention to treat principle, i.e. all participants will be analysed in the intervention group to which they were randomised irrespective of adherence to randomised intervention or protocol deviations. For all outcomes, appropriate summary statistics and differences between groups, e.g. mean differences will be presented, with 95% confidence intervals and p-values from two-sided tests also provided. Where possible intervention effects will be adjusted for the minimisation variables listed in Section **Error! Reference source not found.** Randomisation and Blinding as well as baseline values. No a djustment for multiple comparisons will be made.

14.3 Primary outcome

The primary outcome measure is the 7-day average 24-hour pain score on an 11-point NRS scale (0 = no pain and 10 = worst pain imaginable) measured at 3 months post-randomisation. This is a continuous measure so linear regression methods will be used if the outcome is sufficiently normally distributed (or where data can be suitably transformed), to calculate an adjusted mean difference and 95% confidence interval. The p-value relating to the intervention group parameter as generated by the model will be presented.

14.4 Secondary outcomes

Continuous outcomes will be analysed in a similar way to the primary outcome.

Binary data will be presented as number and percentage. A log-binomial regression model will be used to calculate the adjusted relative risk and 95% confidence interval. The adjusted absolute difference and 95% confidence interval between groups will also be reported. The p-values relating to the intervention group parameter as generated by the model will be presented.

14.5 Planned subgroup analyses

Subgroup analyses will be limited to the same variables used in the minimisation algorithm (see Section 5) and performed on the primary outcome and NPSI only. The effects of these subgroups will be examined by including an intervention group by subgroup interaction parameter in the regression model, which will be presented alongside the effect estimate and 95% confidence interval within subgroups. The results of subgroup analyses will be treated with caution and will be used for the purposes of hypothesis generation only.

14.6 Missing data and sensitivity analyses

Every attempt will be made to collect full follow-up data on all study participants; it is thus anticipated that missing data will be minimal. Participants with missing primary outcome data will not be included in the primary analysis in the first instance (NRS pain score will be considered as missing if fewer than 5 days recorded). This presents a risk of bias, and sensitivity analyses will be undertaken to assess the possible impact of the risk. In brief, this will include a multiple imputation approach.

Further sensitivity analysis will include a per protocol analysis.

Full details will be included in the Statistical Analysis Plan.

14.7 Planned final analyses

The primary analysis for the trial will occur once all participants have completed the 6 month assessment and corresponding outcome data has been entered onto the trial database and validated as being ready for analysis. This analysis will include data items up to and including the 6 month assessment and no further.

15.HEALTH ECONOMICS

A separate Health Economics Analysis Plan will be produced and will provide a more comprehensive description of the planned analyses. A brief outline of these analyses is given below.

15.1 Within-trial economic evaluation

A within-trial health economics analysis will assess the cost-effectiveness of FREMS compared to TENS for patients with PDPN. Initially a cost-consequences analysis will be conducted to describe all important costs and outcomes. Subsequently, a trial-based cost utility analysis from an NHS/personal social services (PSS) perspective will be conducted. The primary outcome for the economic evaluation will be the cost per QALY gained over a 6-month period. The cost-utility analysis will be conducted in line with the NICE Guide to the Methods of Technology Appraisal (2013) [83].

QALYs will be estimated using the EQ-5D-5L questionnaire reported at baseline, month 3 and month 6 and the EQ-5D-5L will be valued using published population tariff values, allowing QALYs to be estimated using the trapezium rule to calculate the area under the curve.

NHS resource use will be measured for each participant over a 6-month period. This will include all medication costs, visits to health services, hospital stays and any social care and community support. Medical costs will be taken from the study medication records, and other NHS resources used will be self-reported by participants. Unnecessary questions in the CSRI will be removed to reduce the burden for participants; however, questions relating to personal costs such as travel costs incurred and time-off-work will be retained for sensitivity analysis. Unit cost data will also be derived from nationally represented sources such as the British National Formulary [84], the National Schedule for Reference Costs [85] and the Unit Costs of Health and Social Care [86]. In order to cost the intervention, the cost of the FREMS machine will be obtained and annuitized given the lifespan of the machine and a discount rate of 3.5%. A cost per patient will then be estimated.

The incremental costs and QALYs of FREMS compared to TENS will be estimated over the 6-month follow-up period and results will be expressed as incremental cost-effectiveness ratios (ICERs). Bootstrapped estimates of the ICERs will be sampled to allow the probability of FREMS being cost-effective to be determined. This will be reported numerically, as well as visually by providing Cost Effectiveness Acceptability Curves (CEACs). Sensitivity analysis will focus on assessing the cost-effectiveness of FREMS from a societal perspective.

15.2 Model-based economic evaluation

In order to assess the long-term cost-effectiveness of FREMS over the lifetime of the patient, a model-based economic evaluation will be conducted. The model will be populated with data (costs, utilities etc.) from various sources, including data obtained from the RCT, literature reviews and expert opinions. A Markov model will be used to estimate the lifetime cost-effectiveness of FREMS. Incremental cost-effectiveness ratios will be estimated and a cost-effectiveness plane as well as a cost-effectiveness acceptability curve constructed. Deterministic and probabilistic sensitivity analysis will be used to assess the robustness of the results obtained from the model.

16.SUBSTUDY

Based on recommendations by the European Medicine Agency for the design of drug trials in chronic neuropathic pain conditions, this trial includes an explorative sub-study to allow stratification according to stimulus evoked pain [49].

Quantitative sensory testing (QST) according to the German Network for Neuropathic pain will assess detection and pain threshold for a variety of sensory qualities [67]. A gain or loss of function can then be determined by calculating z-scores based on values from the normal population. Presence or absence of plasticity changes like central wind-up will also be assessed with the assessment of temporal summation (increased pain to repeated stimuli). We expect to recruit up to 100 patients between Sheffield and Liverpool providing QST data at baseline which can be used to identify a preferential profile for responders to the FREMS treatment [76]. QST will also be able to determine any meaningful recovery or worsening of sensory function 3 months after treatment as a correlate for the safety of the treatment in patients with an underlying neuropathy.

QST is a non-invasive methodology used to assess a patient's somatosensory system function in peripheral neuropathic pain. In this study, QST will be performed following the standardised protocol of the German Research Network on Neuropathic Pain, exploring 11 sensory modalities. It will be performed by the technician trained according to the standards defined by the German Network using equipment already owned by the Trust. The time required for a complete QST is expected to be about

16.1 Sensory testing protocol

A formal standardised QST protocol will be performed according to the German Research Network on Neuropathic Pain protocol. This battery of tests has been extensively validated and has age and gender at birth specific normative ranges. All tests will be performed on a single leg with the same leg used for both baseline and follow up assessments. The testing protocol has the following components:

Thermal Sensations

The tests for thermal sensations will be performed using a TSA 2001-II (MEDOC, Israel) thermal sensory testing device. All thresholds will be obtained with ramped stimuli (1 °C/s) that will be terminated when the subject presses a button. Cut-off temperatures are 0 and 50 °C. The baseline temperature is 32 °C. Cold detection threshold and warm detection threshold will be measured as the threshold temperature able to elicit, respectively, a sensation of cold or warm. Similarly, cold pain threshold, and heat pain threshold will be measured as the threshold temperature able to elicit a painful or distressing cold or warm sensation. For each modality, the mean threshold temperature of three consecutive measurements will be calculated. Later, the thermal sensory limen procedure, consisting of six alternating cold and warm stimuli, will be carried out. The mean temperature span for sensation change and the number of paradoxical heat sensations during the cold stimuli will be recorded.

Mechanical detection threshold (MDT)

This will be measured with a standardised set of modified von Frey hairs (Opti-hair2-Set, Marstock Nervtest, Germany) that exert forces upon bending between 0.25 and 512 mN graded by a factor of 2 (1– 2 s contact time). The contact area of the von Frey hairs with the skin is of uniform size and shape (rounded tip, 0.5 mm in diameter) to avoid sharp edges that would facilitate nociceptor activation. Using the ‘‘method of limits’’, five threshold determinations will be made, each with a series of ascending and descending stimulus intensities. The final threshold was the geometric mean of these five series.

Mechanical pain threshold (MPT)

This will be measured using custom-made weighted pinprick stimuli as a set of seven pin- prick mechanical stimulators with fixed stimulus intensities (flat contact area of 0.2 mm diameter) that exerts forces of 8, 16, 32, 64, 128, 256, and 512 mN. The stimulators will be applied at a rate of 2 seconds on, 2 seconds off in an ascending order until the first percept of sharpness is reached. The final threshold will be the geometric mean of five series of ascending and descending stimuli. This test is designed to detect pinprick hypoalgesia.

Stimulus/response-functions: mechanical pain sensitivity for pinprick stimuli and dynamic mechanical allodynia

Mechanical pain sensitivity (MPS)

This will be assessed using the same set of seven weighted pinprick stimuli to obtain a stimulus–response function for pinprick-evoked pain. Subjects will be asked to give a pain rating for each stimulus on a ‘0–100’ numerical rating scale (‘0’ indicating ‘‘no pain’’, and ‘100’ indicating ‘‘most intense pain imaginable’’). This test is designed to detect pinprick hyperalgesia.

Dynamic mechanical allodynia (DMA)

This will be assessed as part of the test above, using a set of three light tactile stimulators as moving innocuous stimuli: Cotton wisp exerting a force of approximately 3 mN, a cotton wool tip fixed to an elastic strip exerting a force of approximately 100 mN, and a standardised brush (Somedic, Sweden) exerting a force of approximately 200–400 mN. The tactile stimuli will be applied with a single stroke of approximately 2 cm in length over the skin. These stimuli will be inserted into a balanced protocol in between the pinprick stimuli.

A total of 50 stimuli, 15 tactile and 35 pinprick, will be delivered with the subject giving numerical pain ratings for each stimulus. These stimuli will be given in runs of 10, and each run will consist of a different pseudo-random sequence of three tactile and seven pinprick stimuli. All stimuli will be applied with an approximately 10 second inter-stimulus interval – well below the critical frequency for wind-up. Mechanical pain sensitivity will be calculated as the geometric mean of all numerical ratings for pinprick stimuli. Dynamic mechanical allodynia will be calculated as the geometric mean (compound measure) of all numerical ratings across all three different types of light touch stimulators.

Wind-up-ratio (WUR) representing the perceptual correlate of temporal pain summation.

In this test, the perceived intensity of a single pinprick stimulus (128 mN pinprick) will be compared with that of a series of 10 repetitive pinprick stimuli of the same physical intensity (1/s applied within an area of 1 cm^2). The subject will be asked to give a pain rating representing the single stimulus, and the estimated mean over the whole series of 10 stimuli using a ‘0–100’ numerical rating scale. The whole procedure will be repeated five times. Wind-up ratio will be calculated as the ratio: mean rating of the five series divided by the mean rating of the five single stimuli. Wind-up is a frequency-dependent increase in excitability of spinal cord neurons that reaches a plateau after about five stimuli, the perceptual correlate of which can be described by this ratio.

Vibration detection threshold (VDT)

This test will be performed with a Rydel–Seiffer graded tuning fork (64 Hz, 8/8 scale) that will be placed over a bony prominence and left there until the subject cannot feel vibration anymore. Vibration detection threshold will be determined as a disappearance threshold with three stimulus repetitions.

Pressure Pain Threshold (PPT)

This will be performed over the calf muscle with a pressure gauge device (FDN100, Wagner Instruments, USA) with a probe area of 1 cm^2 (probe diameter of 1.1 cm) that exerts forces up to 10 kg/cm^2 corresponding to approximately 1000 kPa. The pressure pain threshold will be determined with three series of ascending stimulus intensities, each applied as a slowly increasing ramp of 25 kPa/s (approximately 0.5 $kg/cm^2/s$).

17. TRIAL ORGANISATIONAL STRUCTURE

17.1 Sponsor

The Sponsor for this trial is University of Birmingham (UoB).

17.2 Coordinating centre

The trial coordinating centre (Trial Office) is Birmingham Clinical Trials Unit (BCTU), based at UoB.

17.3 Trial Management Group

The Trial Management Group (TMG) will take responsibility for the day-to-day management of the trial and will include (but is not limited to) the CI, co-lead, Trial Statistician, Trial Manager, Health Economist and senior BCTU oversight staff. The role of the group is to monitor all aspects of the conduct and progress of the trial, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of the trial itself. The TMG will meet sufficiently frequently to fulfil its function.

17.4 Co-investigator group

The Co-investigator group, an extended TMG, will comprise all members of the co-applicant group and the members of the TMG to review progress, troubleshoot and plan strategically.

17.5 Trial Steering Committee

A TSC will be established for the FREMS-PDPN trial. The TSC will include members who are independent of the investigators, their employing organisations, funders and sponsors. The TSC composition will be chaired by an independent member and will include an independent Statistician, clinicians, health economist and a patient representative.

The TSC will operate in accordance with a trial specific TSC Charter. Membership and duties/responsibilities will be outlined in the TSC Charter. In summary, the TSC will provide overall oversight of the trial including the practical aspects of the trial and ensure the trial is run in a way which is both safe for the participants and provides appropriate data to the sponsor and funder. The TSC will consider and act, as appropriate, upon the recommendations of the DMC.

The TSC will meet at the start of the trial, prior to recruitment of any patients and then will aim to meet at least annually thereafter by videoconference, at face-to-face meetings or via e-mail communication of updates of reports.

17.6 Data Monitoring Committee

The role of the independent DMC is to monitor the trial data, and make recommendations to the TSC on whether there are any ethical or safety reasons as to why the trial should not continue or whether it needs to be modified. To this end, data on safety outcomes and (where appropriate) primary and major secondary outcomes will be supplied to the DMC during the trial.

Data analyses will be supplied in confidence to a DMC, which will meet prior to trial commencement to agree the manner and timing of such analyses. The DMC will be asked to give advice on whether the accumulated data from the trial, together with the results from other relevant research, justifies the continuing recruitment of participants. The DMC will operate in accordance with a trial specific DMC Charter. The DMC will meet at least annually as agreed by the Committee and documented in the Charter.

Additional meetings may be called if recruitment is much faster than anticipated and the DMC may, at their discretion, request to meet more frequently or continue to meet following completion of recruitment. An emergency meeting may also be convened if a safety issue is identified. The DMC may consider recommending the discontinuation of the trial if any issues are identified which may compromise participant safety. The DMC may recommend early stopping of the trial if the interim analyses show differences between treatments that are deemed to be convincing to the clinical community. Further details on the trial stopping guidelines will be outlined in the DMC Charter and the Statistical Analysis Plan.

17.7 Finance

The research costs of the trial are funded by a NIHR Health Technology Assessment (HTA) grant, reference NIHR133599, awarded to Dr Bernhard Frank and UoB. The trial has been designed to minimise extra 'service support' costs for participating hospitals as far as possible. Additional costs, service support costs and excess treatment costs associated with the trial, e.g. gaining consent, are estimated in the Schedule of Events Cost Attribution Template. These costs should be met by accessing the Trust's Support for Science budget via the Local Comprehensive Research Network. Participants will be reimbursed up to £10 travel costs for each trial specific visit.

18. ETHICAL CONSIDERATIONS

The trial will be conducted in accordance with the UK Policy Framework for Health and Social Care Research and applicable UK Acts of Parliament and Statutory Instruments (and relevant subsequent amendments), which include Data Protection Act 2018; and the Principles of GCP as set out in the UK Statutory Instrument (2004/1031; and subsequent amendments). The protocol will be submitted to and approved by the REC prior to the start of the trial.

Before any participants are enrolled into the trial, the PI at each site is required to obtain the necessary local approval.

It is the responsibility of the PI to ensure that all subsequent amendments gain the necessary local approval. This does not affect the individual clinicians' responsibility to take immediate action if thought necessary to protect the health and interest of individual participants.

19. CONFIDENTIALITY AND DATA PROTECTION

Personal data and sensitive personal data recorded on all documents will be regarded as strictly confidential and will be handled and stored in accordance with the Data Protection Act 2018 (and subsequent amendments).

Participants will only be identified by their unique trial identification number and initials on CRFs (except the ICF and Randomisation form) and on any correspondence with the Trial Office. For all participants full name, full date of birth, gender at birth and NHS number will be collected on the Randomisation Form. The participant's full name will also be collected on the participant consent forms in addition to their email address and/or mobile number.

Participants will acknowledge the transfer and storage of their informed consent form to the Trial Office. This will be used to perform central monitoring of the consent process.

The PI must maintain documents not for submission to the Trial Office (e.g. Participant Recruitment and Identification Logs) in strict confidence. In the case of specific issues and/or queries from the regulatory authorities, it will be necessary to have access to the complete trial records. Representatives of the FREMS-PDPN trial team and sponsor may be required to have access to participants' notes for quality assurance purposes, but participants should be reassured that their confidentiality will be respected at all times. The Trial Office will maintain the confidentiality of all participant data and will not disclose information by which participants may be identified to any third party.

20. FINANCIAL AND OTHER COMPETING INTERESTS

There are no financial or other competing interests related to the results of this trial. Members of the TSC and DMC are required to provide declarations on potential competing interests as part of their membership of the committees. Authors are similarly required to provide declarations at the time of submission to publishers.

21. INSURANCE AND INDEMNITY

UoB has in place Clinical Trials indemnity coverage for this trial which provides cover to UoB for harm which comes about through the University's, or its staff's, negligence in relation to the design or management of the trial and may alternatively and at UoB's discretion provide cover for non-negligent harm to participants.

With respect to the conduct of the trial at Site and other clinical care of the patient, responsibility for the care of the patients remains with the NHS organisation responsible for the Clinical Site and is therefore indemnified through the NHS Resolution.

22. ACCESS TO FINAL DATASET

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 six 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 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 transfer of participant identifiable information. Any data transfer will use a secure and encrypted method.

23. PUBLICATION PLAN

On completion of the trial, the data will be analysed, and a Final Study Report will be prepared. Results of this trial will be submitted for publication in a peer reviewed journal. Manuscripts will be prepared by the writing group as defined in the trial publication plan. Any secondary publications and presentations prepared by Investigators must be reviewed and approved by the TMG. Manuscripts must be submitted to the TMG in a timely fashion and in advance of being submitted for publication, to allow time for review and resolution of any outstanding issues. Authors must acknowledge that the trial was performed with the support of NIHR HTA, UoB and BCTU. Intellectual property rights will be addressed in the Clinical Trial Site Agreement between Sponsor and site.

Results will also be sent to all participating centres who will notify the participants recruited from their site. Participants will be invited to discuss the study results with the local research team.

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