<<Insert local letterhead>>

Participant Information Sheet

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

1. Invitation and brief summary

We would like to invite you to take part in a clinical trial (research study). We are looking at whether a nerve stimulation device can reduce pain from the nerve damage caused by diabetes.

Joining this study is completely voluntary and your decision will not affect your standard of care in any way. Before you decide we would like you to understand why we are doing this research and what it will involve. Please take your time to read through this information carefully. Discuss it with your friends and family if you wish.

This information sheet tells you why we are doing the study, what will happen to you if you take part and detailed information about how it will be run. Please do get in touch with us if you have any questions or if any of the information is unclear.

2. Why are we doing this research

Peripheral neuropathy is a common complication of diabetes and happens because of nerve damage in the feet and legs. Patients with neuropathy may have pain, discomfort or loss of feeling in the areas affected. The pain caused by peripheral neuropathy can badly affect sleep and quality of life.

The standard treatment for nerve pain is medication but this doesn't always work in some patients and there can also be side effects and problems tolerating the drugs.

In this trial we are going to test a treatment called FREMS for adults with Painful Diabetes-Related Peripheral Neuropathy (PDPN). We hope that FREMS treatment will reduce pain, and improve sleep quality and overall quality of life.

Participants will be randomly allocated to a treatment with a 50:50 chance of getting either of the two treatments:

- FREMS: Frequency Rhythmic Electrical Modulation System
- TENS: Transcutaneous Electrical Nerve Stimulation.

Neither you nor your doctor will choose which you get. This is done so that both groups of patients are as similar as possible except for the treatment they receive. The rest of your treatment will continue as normal.

3. What are the treatments?

What is TENS?

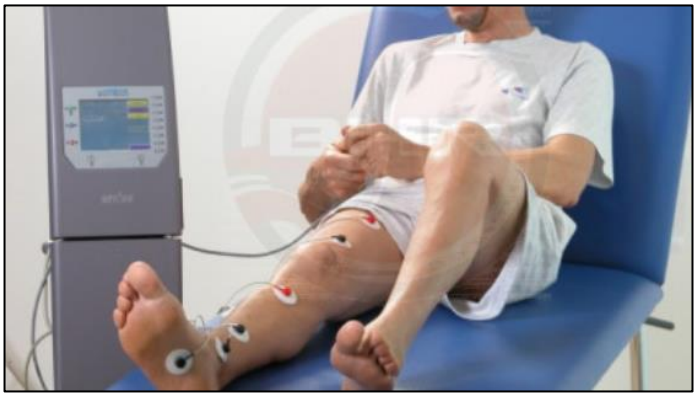

Figure 1: FREMS/TENS machine used in FREMS-PDPN

TENS is used quite commonly in the NHS for pain relief in various conditions such as arthritis and endometriosis. In this study we will be giving TENS treatment using an APTIVA® device. It works with 8 electrode pads that stick to the skin on the feet and legs. These deliver electrical pulses with a fixed frequency to stimulate nerve ends just under the skin in the affected area. This can potentially reduce the transmission of pain signals to the brain and spinal cord.

What is FREMS?

FREMS looks very similar to TENS. In this study we will be giving FREMS treatment using the same APTIVA® device as for the TENS treatment. It also uses 8 electrode pads stuck to the skin giving electrical pulses to stimulate the nerve ends. The difference is that FREMS delivers an electrical pulse with a different type of changing frequency.

Evidence suggests both TENS and FREMS might work for pain in the short term, but we are hoping this trial will tell us if FREMS helps nerve pain better and for longer than TENS. Both treatments are safe.

At each treatment session, the electric pulse level is set by the nurse, based on what the patient feels. Usually the electrical stimulation can be felt as a kind of buzzing, but it shouldn't be painful.

This trial is blinded, which means neither you nor your doctor will know which treatment you get. This helps to make the results as reliable as possible.

4. Why have I been invited?

You have been invited because you have diabetes and still have painful peripheral neuropathy despite taking medication for it.

5. What would taking part involve?

SCREENING

If you want to take part in the trial we will ask you to give consent using an online screening consent form. This can be done at your clinic visit or at home on a personal device. We will ask you to complete a 7 day pain diary. You will get reminders to send this score by text message every day for a week.

We will ask you to let the team at your hospital access your medical records. This will then let your research centre know you are happy to enter a process known as screening. The screening part of

the trial lets your doctor or nurse get more information about you to check if you can take part and if the trial will be suitable for you.

When the screening phase is complete your study team will contact you with the results. If your 7 day pain score is not within the range suitable for the trial your healthcare team will let you know and discuss standard of care treatment with you.

If you are potentially eligible for the rest of the trial your study team will arrange a visit for you in person.

FIRST VISIT

At this visit you have the opportunity to ask any questions you might have. You will then be given some time to think about what you would like to do. If you decide you would like to participate you will be asked to sign and date the online main consent form. The doctor or nurse will also sign this and give you a copy (or you can receive it by email).

During this first visit you will be asked some questions about your medical history and a clinical exam will be done by your doctor. This is to help the research team check you are eligible to take part. You will be asked to complete a set of questionnaires about your pain, sleep, mood and general health and wellbeing. The nature of some of the questions asked may be sensitive and include questions about depression and thoughts of suicide. Should your answers reflect suicidal tendencies the research team has a duty of care to make your clinical care team aware. There will be a built-in trigger alert within the electronic questionnaire database that will inform your care team of your answers, should you flag as a risk. If this is the case they will contact you directly to discuss your health needs.

Your blood pressure and height and weight will be checked. You may also be asked to give a blood sample depending on when the last one for your diabetes was taken. This sample will be approximately 4mls, roughly the same amount as a teaspoon. If you have had a blood test in the past two months, consent will be sought to access this and use for eligibility purposes.

RANDOMISATION TO A TREATMENT

Once all screening and baseline procedures have been done and eligibility has been confirmed by your doctor you will be randomised using an online system. Neither you, your clinical care team or the research team will have any control over who receives which treatment. The central study team will do this.

PAIN DIARY

As you did during the screening phase of the trial, we will ask you to keep a pain diary by submitting a daily score, every day for 6 months. You will do this in the same way as during the screening part of the trial, by text message. The service provider for this will be a company called FireText. FireText is accredited on the NHS Data Security and Protection Toolkit and will only store your anonymised trial ID and your telephone number.

TREATMENT SESSIONS

The device used in this study gives both FREMS and TENS treatment. It is operated with a numbered key card pre-programmed with your randomised allocation. The team will follow the same treatment procedures for all participants to make sure the study remains blinded.

The treatment will be for 10 sessions of about 35 minutes each. You will be asked to come into the hospital for all of your treatment. It's important to try to attend all 10 sessions as you might not feel any benefit until all the treatment is completed.

When you arrive for your treatment your study nurse will show you the device and explain the procedure. You will be asked to lie down and 8 sticky pads will be put on your legs (calf muscle, shin bone, ankle and foot). The key card will select which treatment is given. Electric nerve stimulation will be transmitted through the pads and will be slowly increased. It should get to the point that you can feel the stimulation without finding it uncomfortable. Your study nurse will remain with you and monitor you closely during treatment.

After 35 minutes your treatment session will be finished, and you can go home. You will then come back for your next pre-scheduled session. Your treatment schedule should be 5 sessions a week over a two-week period.

Figure 2: Summary of the visits, who will be conducting them and how long they should take

Visit in clinic or via telephone/video-call	Time taken	Conducted by
First visit		
• Sign main consent form • Complete health questionnaires online or on paper • Research team will collect your personal details, medical history and pain medication history • The doctor will perform a clinical physical exam • Measure height and weight • Check blood pressure • Enter you into the trial and allocate your trial treatment. • Start first session of trial treatment (within a week of being randomised if not at the first visit)	Around 90/120 minutes	Your research team
Treatment visits (Ten sessions over a two week period)		
• Administer treatment • Monitor for any side-effects of medication • Complete questionnaire on last treatment session.	50 minutes per session	Your clinical care team
3 Month visit		
• Complete questionnaires online • Medication review	About 50 minutes	Your research team
6 month visit		
• Medication review • Clinical exam • Complete questionnaires online	Up to 60 minutes	Your research team
End of trial participation		

AFTER YOUR TREATMENT

On your final treatment sessions, you will be asked to answer some of the same questionnaires you completed before your treatment started.

You will then be contacted 3 and 6 months after randomisation to complete all the same questionnaires you completed at baseline.

6. Optional Sub study

In Sheffield and Liverpool we are doing a sub study to look more closely at a non-invasive method used to assess patients' sensory function in peripheral neuropathic pain. This will then help us identify which patients may respond best to FREMS treatment. The information from this test will also determine any recovery or worsening of sensory function after FREM treatment is completed.

If you are willing to take part in this sub study, we would like to perform Quantitative sensory testing (QST) at baseline and 3 months post-randomisation. QST measures changes in sensitivity to sensations such as pressure and temperature.

This test will be performed by a trained doctor or research nurse. During the test patients will be exposed to different temperatures via sensors that have been placed on the skin. You will be asked to push a button when you feel a change in temperature.

The researcher will also use different textured probes and ask you how they feel on your skin. The test should take about 60 minutes to complete. It should not feel uncomfortable and is perfectly safe with no related side effects. You have the right to stop the test at any point should you wish.

7. What are the possible benefits of taking part?

Both treatments could give you some pain relief. You will receive a thorough check of your condition and could try a new therapy before it is generally available. While there may be no immediate benefits to you, the aim is to improve care for people with pain from their diabetes.

8. What are the possible disadvantages and risks of taking part?

Ten sessions of treatment and completing the questionnaires can be time consuming. There are no side effects expected from either TENS or FREMS treatment but pain or discomfort during the nerve stimulation is possible. This will be monitored and minimised by your study nurse.

9. Who is organising and funding the research?

The study is sponsored by the University of Birmingham, which means the University of Birmingham has certain legal and ethical responsibilities for the study. It is being coordinated by Birmingham Clinical Trials Unit and is funded by the government through the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme (ref: NIHR133599). The chief

investigator for the trial is Dr Bernhard Frank, based at The Walton Centre NHS Foundation Trust, Liverpool.

10. How have patients and the public been involved in this study?

This research topic was discussed with both patients and members of the public, as well as patients via local diabetes groups. The patients who were involved in the discussions included patients with PDPN who received and did not receive FREMS treatment as well as patients' carers. The patient and public group (PPI) were very supportive of the research questions and the design.

A member of this PPI group is also one of the researchers and will continue to be involved in the conduct of the research.

The conduct of the trial is entirely in the hands of very experienced researchers and no PPI group or lay person has any access to your personal healthcare records, or is able to influence your treatment.

11. Who has reviewed the study?

All research which takes part in the NHS is looked at by an independent group of people who protect patient interests. This group is called a Research Ethics Committee. Before we asked any patients to join, the trial was reviewed and approved by Bromley Research Ethics Committee.

12. Involvement of your GP

With your permission we will tell your GP that you are taking part in the study.

13. Will my taking part in this study be kept confidential?

Yes. Your participation in the study and all information collected will be subject to the General Data Protection Regulation and the Data Protection Act (2018) and will be kept strictly confidential.

We will need to use information from you and your medical records for this trial. This information will include:

- Your Name
- Date of Birth
- NHS number
- Contact details
- Gender at birth

People will use this information to do the research or to check your records to make sure that the research is being done properly.

People who do not need to know who you are will not be able to see your name or contact details. Your data will have an anonymised participant ID number instead. We will keep all information about you safe and secure.

Once we have finished the trial, we will keep some of the data so we can check the results. We will not share any data that can identify you with any third party.

Your study doctor or research nurse may also need to send a copy of your Consent Form to other healthcare professionals (e.g. your GP) to prove that you have given consent to take part.

By taking part in the study you will be agreeing to allow authorised representatives from the sponsor to look at your study records including your medical records. This is to ensure the study is being conducted to the highest possible standard.

Once the trial is finished, we may want to get information about your progress from national health registries, for example to check for use of pain medication or other services for up to 10 years after the end of the trial to see if they are reduced. If you consent to it, the central research team may, in the future, access electronic data from your central NHS records, such as NHS Digital or Hospital Episode Statistics. This would give us information that is routinely collected during your visits to your GP and hospital, and lets us find out about your health and use of NHS services after the trial has ended without contacting you further. To do this, we would send your name, gender, date of birth and NHS number with any request for information. You may withdraw your consent for researchers to access electronic data from your central NHS records at any time without giving a reason by speaking with your consultant or the researcher who recruited you onto the trial.

At all times, authorised individuals will have a duty of confidentiality to you as the research participant. The study data which we generate and responses from study questionnaires will only be identified by the allocated unique study number.

14. What will happen to the data I give?

We will ask for your consent before collecting your personal data listed in the table below. This is only for use in the trial and we will try to make this as non-invasive as possible.

When	What data will be collected
Screening visit	• Full name (first, middle & surname) • Email address (if you opted for a copy of the consent form to be e-mailed to you) • Mobile phone number (for daily pain score texts)
First visit (baseline)	• Full date of birth, gender, NHS number • Contact details: email address and/or mobile phone number • Relevant medical history • Current medications you are taking • Physical exam and questionnaires completed during this visit
Follow-up visits at 3 months	• Questionnaires completed online or during this visit
Follow up visits at 6 months	• Questionnaires completed during this visit • Current medication and medical history • Physical exam

Who is the data controller?

The University of Birmingham, Edgbaston, Birmingham B15 2TT is the data controller for the personal data that we process in relation to you. This means that the University is responsible for looking after your information and using it properly.

What are your choices about how your information is used?

You can stop being part of the trial at any time, without giving a reason, but we will keep information about you that we already have.

We need to manage your records in specific ways for the research to be reliable and accurate. This means that we won't be able to let you see or change the data we hold about you.

The University takes great care to ensure that personal data is handled, stored and disposed of confidentially and securely. Staff receive regular data protection training and the University has put in place organisational and technical measures so that personal data is processed in accordance with the data protection principles set out in data protection law. More information on how the University processes personal data can be found on the University's website on the page Data Protection – How the University Uses Your Data (http://www.birmingham.ac.uk/privacy/index.aspx).

How will my personal data be kept secure?

The University of Birmingham takes great care to ensure that personal data is handled, stored and disposed of confidentially and securely. Our staff receive regular data protection training, and the University has put in place organisational and technical measures so that personal data is processed in accordance with data protection law.

Any physical paperwork containing identifiable data will be kept in an access-controlled and secured room inside a locked filing cabinet. Electronic data will be kept on secure, encrypted IT servers at the University of Birmingham.

How long will my personal data be kept?

Your data will be kept for at least 10 years after the publication of the research.

Where can I find out more about how my information is used?

You can find out more about how we use your information

- at www.hra.nhs.uk/information-about-patients/
- in the leaflet available from www.hra.nhs.uk/patientdataandresearch
- by asking one of the research team
- by contacting the University of Birmingham Data Protection Office:

The Data Protection Office, Legal Services, The University of Birmingham, Edgbaston, Birmingham B15 2TT. Email: dataprotection@contacts.bham.ac.uk. Telephone: 0121 414 3916

15. What if something goes wrong?

We do not expect any problems as a result of your participation in the trial. However, all patients are covered for negligent harm according to NHS indemnity guidelines. If you have a concern about any part of this trial, you should ask to speak to a member of the research team who will do their best to answer your questions. The University of Birmingham also arranges clinical trial insurance which is renewed annually and provides cover to the University for harm which comes about through the University's, or its staff's, negligence in relation to the design or management of the trial.

If you wish to complain about any aspect of the way you have been approached or treated during this trial, the normal NHS complaints mechanisms will be available to you. If you wish to complain about how you have been treated during this trial please contact the Patient Advice and Liaison Service (PALS) or the Complaints Team at your local hospital. The contact details can be found on the end of this Information Sheet.

16. What if I do not want to take part?

Participation in the study is entirely voluntary and if you decide not to take part you do not have to give a reason for this. If you do choose to enter the study you are free to change your mind and withdraw at any point.

The standard of care provided to you by your doctor will not be affected in anyway should you decide not to participate.

17. Will my travel expenses be reimbursed?

Yes, we can help towards your travel expenses for trial visits to the hospital. A travel cost limit of £10 per visit is provided. Please speak to your research team about this.

18. What happens if new information becomes available?

Sometimes we get new information about the treatment being studied. If this happens, a member of the research team will tell you and discuss whether you should continue in the study. If your research doctor is happy for you to continue in the study, you will have the option to decide whether to continue. A member of the research team may ask you to re-sign a consent form if you do.

If you decide not to carry on, a member of the research team will make arrangements for your standard clinical care to continue.

Sometimes your study doctor might consider it to be in your best interest to withdraw you from the trial. If this is the case they will explain their reasons for this and arrange your continuing care.

If for any reason the study is stopped, you will be informed and your continuing care arranged.

19. What happens when the research study stops?

At the end of the study your doctor will continue to look after you and your treatment.

20. What will happen to the results of the research study?

Once the study is completed and the data is collected and analysed we will publish our results in medical journals, to help other doctors to learn, and patients to benefit. This will be in an anonymous way so you cannot be identified. Names and participant details won't be included in the results.

21. Do you have any further questions?

You will have some time to think about the study and make your decision. You may wish to discuss it with your family or friends. If you take part, you will receive a copy of this information sheet and a copy of the signed Consent Forms. If, at any time, you have any questions about the study you should contact your study doctor or research nurse using the details below.

Thank you for taking the time to read this information sheet.

Contact Information

If you would like to speak to someone about the study please contact:

< Contact Name > <Job Title>

<Telephone and/or E-mail>

Support can also be found through *<NHS Patient Advisory and Liaison Service (PALS); or local equivalent>*

Tel: *<insert local PALS contact number(s)>* Email: *<insert local PALS email address>*

Alternatively, you can contact the FREMS-PDPN trial team:

FREMS-PDPN trial office
Birmingham Clinical Trials Unit
Public Health Building
University of Birmingham
B15 2TT
Email: frems-pdpn@trials.bham.ac.uk

This study is funded by the National Institute for Health Research (NIHR) Heath Technology Assessment programme (project reference NIHR133599 The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.