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PARTICIPANT INFORMATION SHEET

Diabetic Peripheral Neuropathy Treatment with Dorsal Root Ganglion Stimulation – the PENTAGONS Trial

We would like to invite you to take part in our research study. Before you decide whether you would like to do so it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish.

There is no obligation to take part in this research study and choosing not to will not affect the quality of your care in any way.

Thank you for reading this information sheet.

What is the purpose of the study?

The purpose of the study is to compare Dorsal Root Ganglion Stimulation (DRGS) with continued medical management (CMM) in patients with Painful Diabetic Neuropathy (PDN) affecting their feet.

DRGS is a treatment for some types of severe pain that is not controllable by medication alone. On each side of the spine along its length from the top of the neck to the bottom of the back, there are about 30 "nerve roots" that connect the spinal cord to different parts of the arms, body, and legs. These nerve roots carry signals coming down from the brain that control your muscles, and they also carry sensory signals back in the other direction, including pain signals. At the point where each nerve root enters the spine it has a bulge called the "dorsal root ganglion" or DRG. This is a key part of the pathways that carry pain signals, and it has been found that electrical stimulation applied to the DRG can block pain signals coming from the specific area of the body that the nerve root is running to.

DRGS has been used to treat several types of pain in the legs and feet. However, it has never been tested in a trial for Painful Diabetic Neuropathy. Testing in clinical trials is important because it is the best way to tell for sure whether, and how well, a treatment works.

What does the treatment involve?

Half of all patients who join the study will continue to receive their existing pain relieving drug treatment, which is referred to as continued medical management (CMM).

The other half of the patients will undergo surgery. Wires are inserted into the lower back through a needle. This procedure is similar to the procedure for giving an epidural anaesthetic (as used for example for pain relief in childbirth). The wires are then connected to a 'pulse generator' that is implanted under your skin. The pulse generator is a small box rather like a heart pacemaker, which contains a battery and some electronics to generate small pulses of electricity that pass down the wires to electrical contacts at the wire tip, where they continuously stimulate the DRG. The procedure typically takes between 45 and 90 minutes although some cases may take longer. It is performed under local anaesthesia, with sedation to ensure that you are comfortable.

Why have I been invited to take part in the study?

You have been invited to take part in this study because you have severe pain due to diabetic neuropathy, and the pain is not well controlled with standard medications. To be eligible for the study you must have tried at least the following medications:

- at least one of gabapentin or pregabalin, and
- at least one of amitriptyine or duloxetine

The types and doses of any pain relieving medications you are taking must be stable (i.e. no pain relieving drugs are being introduced or stopped) at the time of enrolment.

We are aiming to recruit a total of 56 patients with symptoms similar to yours.

Do I have to take part?

No. It is up to you to decide whether or not to take part. We have provided you with this information sheet, which we hope will enable you to make a decision. We are very happy to discuss this further in person or over the phone if you have any questions or concerns. If you do decide to take part, you are free to withdraw at any time, without giving a reason. A decision to withdraw will not affect the standard of care you receive.

What will happen to me if I decide to take part?

We will go through the information in this sheet with you again, and give you another opportunity to ask questions. If you still wish to proceed we will ask you to complete a study consent form.

We will then ask you to complete some questionnaires about your pain and the effect it is having on your quality of life. We will check what medications you are taking including the name and dose of your tablets (we may ask to see a copy of the repeat prescription forms from your GP).

We will then use a computer system to randomly choose whether you receive the DRGS implantation surgery or continue on your medical management (CMM). This will be on a

50/50 basis, i.e. half of the patients in the trial will be allocated DRGS and half will be allocated CMM.

If you are randomised to surgery, we will arrange a clinic visit before the operation in order to perform any necessary tests to ensure that surgery is safe. Usually this will include a blood test and an electrocardiogram ('heart tracing') and a physical examination. We will also arrange an MRI scan of your lower back. This is done in order to ensure that there is enough room for the stimulator wire next to each dorsal root ganglion. (If you happen to have had an MRI of this area which meets the standards we require, within the last 12 months, we may not need to repeat this).

On the day of surgery we will admit you and explain the procedure and its risks again, and complete a consent form for the operation. We will then carry out the procedure as described above to implant the stimulator wires and pulse generator. We will test the system during the procedure to ensure that it is providing stimulation that covers your area of pain.

After the operation, your stimulator system will be switched on. Once you are comfortable you will be able to go home. Usually this is the day after surgery. We will see you two weeks after surgery in order to check on your wounds and adjust the system settings if needed.

For both groups in the trial, we will ask you to complete the pain and quality of life questionnaires three more times during the next six months. These will be 8 weeks, 18 weeks, and 30 weeks from the day you were allocated to surgery or CMM. We will administer these questionnaires online if possible, but paper versions will be available if you prefer not to do it online. Paper versions will be sent in the post and you will be provided with prepaid envelopes to return the paperwork back to us. In addition to these simple questionnaires, you will be asked to complete a simple diary to record the medications you use, any visits to doctors, nurses or other healthcare professionals, and whether there were days when your pain prevented you doing your usual activities. The diaries will be on paper and we will provide prepaid envelopes to return them (Please refer to the Study flowchart on page 11 for further information).

The questionnaires will take approximately 30-60 minutes of your time to complete on each occasion. If necessary we may telephone to remind you to return them. In order to allow the trial office to arrange online questionnaire completion, to send paper versions to you in the post, and to contact you if we need to remind you to complete any of the questionnaires, we will ask for your address, email address, and telephone contact details. This information will be kept securely, separately to your clinical information, and accessible only to the study team. Please see the section below entitled "Will my taking part in the study be kept confidential?" for further details.

If you are allocated DRGS, but the preoperative assessments show that you cannot undergo surgery (for example because the MRI shows that there is not enough room for the electrode) we will follow you up as if you had been allocated CMM.

If you were initially allocated CMM, but the trial shows that DRGS does work, then you will be offered DRGS treatment as soon as the study is complete and the data has been analysed and reported.

Are there any possible disadvantages or risks from taking part?

The operation that we will do is exactly the same as what we do routinely for patients with pain of other types in the feet. There are risks involved with any surgical treatment and it is important that you are aware of the risks of DRG stimulation before you decide whether or not to participate in this trial.

The risks of DRGS surgery include:

- Infection: In people without diabetes who are having similar stimulator implants for other types of pain, the risk of an infection of the stimulator system is about 1 person in every 25. In people with diabetes, the extra sugar in the bloodstream may make infection more likely. If the stimulator system gets infected it has to be removed. If it was very effective before it was removed, then we can replace it a few months later once we are certain that the infection has cleared completely.
- Lead migration: The stimulator wires have to be in a precise position in your back, right next to the DRG. It is possible for them to slip slightly out of place ('migration') which can result in the loss of pain relieving effect. The chance of this happening with DRGS is not exactly known, but may be up to 1 in 5. If this happens, we can replace the lead.
- Cerebro-Spinal Fluid (CSF) leak (less than 1 in 100): The nerves in the spine are contained within a sheath (a kind of cover), and within that sheath they are surrounded by a watery fluid called 'CSF'. The stimulator wires are positioned outside that sheath and the electrical pulses pass through the sheath to get to the DRG. Sometimes there can be a leak of the CSF through the sheath, and this can cause a headache after the operation. Usually this settles down within a few days, but occasionally it persists. If so, it can be treated with an injection in the back to seal up the leak.
- Nerve injury (less than 1 in 100): This can be due to direct injury whilst the lead is being put in, or to bleeding around the nerves.
- Other risks (less than 1 in 100): You will be having sedation and lying still for a period while the system is implanted. This carries a small risk of complications including blood clots forming in the legs (known as 'deep vein thrombosis' or DVT).

Getting the stimulator wires into the right place requires the use of X-rays so that we can see where the wires are inside your back. This procedure is part of your routine care. If you take part in this study you will not undergo any additional procedures requiring Xrays. This procedure uses ionising radiation to form images of your body. Ionising radiation can cause cell damage that may, after many years or decades, turn cancerous. The chances of this happening to you are the same whether you have DRGS in the study or outside it. X-rays can harm a developing baby so you cannot have DRGS if you are, or might be, pregnant.

Assessment for possible DRGS includes having an MRI scan of your lower back. There is a small chance that this could show something unexpected. In the unlikely event that this happens, we will discuss with you the nature and significance of what has been found, and if it needs

further investigation or treatment we will arrange a referral to a relevant specialist, either directly or through your GP.

What are the possible benefits of taking part?

If DRGS is effective for diabetic neuropathic pain, then it is likely that if you have the treatment your pain will be improved. However, it is important to be aware that even if the treatment is effective for most people, it may not work in every case.

We hope that the information we get from this study will give us accurate information about how effective DRGS is in painful diabetic neuropathy. This information will help us to guide future patients about how effective DRGS is likely to be for them, and we hope this will help them to decide whether they wish to have DRGS.

Are there any things I will not be able to do with an implanted stimulator system?

There are a few things that you should avoid, or exercise caution when doing, after you have had a stimulator system implanted. These include:

- Flying is safe but you should take care when approaching airport security devices, as these can turn off your device or reset it. Your device may also set the alarms off. You should show your device identification card, which will be given to you when you leave hospital. You can then request a hand search instead of walking through the security gate. Security personnel can use a handheld security wand, but ask them not to hold the wand near the battery any longer than is needed. If you must pass through a security screening device then follow this procedure:

    1. Using your handheld controller, turn your system OFF.
    2. Approach the centre of the security device and walk through normally.
    3. After you pass through the security device, turn your system ON again to resume therapy.

- You must turn OFF your stimulator while you drive.
- Pressure changes can damage the battery. For this reason you should not go scuba diving below 10 metres (33 feet) or enter a hyperbaric chamber above 2.0 atmospheres. High altitude activities (e.g. skiing, skydiving) are safe in this regard (however, please see the next point below).
- Most other work and leisure activities are safe. However please bear in mind that your stimulator leads will run from your low back, under the skin, to the battery which is usually under the skin in the upper part of the buttock or your side. Although it is made of flexible and durable material, excessive bending or twisting movements in this region can dislodge the lead from the dorsal root ganglion or risk damaging it. You may then need surgery to replace the lead.

- Please speak with your neuromodulation team before undergoing any future medical procedures. If you need to have an emergency procedure and are not able to contact us beforehand, you will need to make sure your device is turned OFF before the procedure starts and you should let the doctors treating you know that you have an implanted stimulator system. This is to prevent interference from other medical equipment.
- There are restrictions associated with having a Magnetic Resonance Imaging (MRI) scan if you have a DRG stimulator. If an MRI scan is suggested, please make sure that the doctors treating you know that you have a stimulator implant, and speak to your neuromodulation team for advice.

Will my General Practitioner/family doctor (GP) be informed of my participation?

We will inform your GP about your participation in this study.

Will my taking part in the study be kept confidential?

All the information that is collected about you during the course of the research will be kept strictly confidential.

You will be given a unique participant number and all data and results will be stored using this, instead of your name or any other identifiable personal information, and under password protection. A document linking identifiable personal information (including participant names, addresses, email addresses, and telephone numbers) to ID numbers will be stored separately, on a secure University of Oxford network database, password-protected and accessible only by the study team. It will not be possible for anyone else to identify the results as yours.

Responsible members of the University of Oxford and relevant NHS Trust may be given access to data for monitoring and/or audit of the study to ensure that the research is complying with applicable regulations.

What will happen to my data?

The University of Oxford is the sponsor for this study based in the United Kingdom. We will be using information from you and/or your medical records in order to undertake this study and will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly. The University of Oxford will keep identifiable information about you for 6-12 months after the study has finished. This excludes research documents with personal information such as consent forms, which will be held for ten years.

Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally-identifiable information possible

You can find out more about how we use your information at octru.ox.ac.uk and/or by contacting octrutrialshub@ndorms.ox.ac.uk.

Your study site will collect information from you and/or your medical records for this research study in accordance with our instructions. Your study site will use your name, NHS number and contact details to contact you about the research study, and make sure that relevant information about the study is recorded for your care, and to oversee the quality of the study. Individuals from the University of Oxford and regulatory organisations may look at your medical and research records to check the accuracy of the research study. Your study site ill pass these details to the University of Oxford along with information collected from you and/or your medical records. The only people in the University of Oxford who will have access to information that identifies you will be people who need to contact you to carry out study follow-up or audit the data collection process. The people who analyse the information will not be able to identify you and will not be able to find out your name, NHS number, or contact details.

Your study site will keep identifiable information about you, from this study, for 6-12 months after the study has ended.

Will I be reimbursed for taking part?

Some of the assessments will be done when we are seeing you anyway as part of your treatment. For any extra visits that you make as part of the study we will reimburse your travel expenses fully using standard business mileage costs for car travel and any parking costs.

What will happen to the samples I give?

The blood samples taken at the preoperative assessment (patients undergoing DRGS only) are only used for routine preoperative health check purposes and are not used for any other research purpose. These samples are routinely destroyed by the hospital laboratory after use.

What will happen if I don't want to carry on with the study?

You are free to withdraw at any time, without giving a reason. A decision to withdraw at any time, or a decision not to take part will not affect your future care in any way. If you wish to withdraw from trial treatment (for example, if you are allocated to DRGS but decide you do not wish to have it) we would still like to follow you up if possible and will ask your permission

to continue to collect and use routine follow-up data for trial purposes. However if you do not wish to contribute any further data to the trial we will respect that.

In addition, we may withdraw you from the trial in some circumstances, including:

- Ineligibility (either arising during the trial or retrospectively having been overlooked at screening)
- If you develop another medical condition which requires removal of the implanted device or results in inability to continue to comply with trial procedures such as follow up questionnaires
- If you develop another condition that means you are no longer able to give valid consent
- If for any other reason there is a significant deviation from the trial protocol
- If we become unable to contact you

In all of these cases we will keep and use data up to the point where participation was discontinued.

If you withdraw or are withdrawn from the trial after having had DRGS, the neuromodulation team will follow you up outside the trial as per routine practice. If you withdraw or are withdrawn from the trial but have not had DRGS, we will refer you back to your GP and diabetologist for ongoing care.

If participation is discontinued due to an adverse event, we will arrange for follow-up visits or telephone calls until the adverse event has resolved or stabilised.

What will happen to the results of this study?

We hope that the results of this study will be suitable for scientific publications in biomedical journals as well in presentations at national and international conferences. We will also send you a newsletter at the end of each year to update you on the study progress. At the end of the study we will send you the final summary of our results.

Please note that it will never be possible to identify you or your individual data from any report or publication placed in the public domain.

Data will be kept **in anonymous form** after this study is complete in case it proves useful in future studies. The standard period for retention for studies at the University of Oxford is 10 years.

What if you find something unexpected?

If by coincidence members of the study team see anything that leads us to think you might have an unrelated medical condition, you will be informed of this and we will advise you to discuss it with your General Practitioner (GP).

What if there is a problem?

If there are any problems or you have any complaints during the course of this study, you should contact *(Professor James FitzGerald via his PA Vicky Ford on 01865 234605).*

If you are still unhappy you can contact your local hospital's Patient Liaison Service *(Insert details e.g. Oxford University Hospitals NHS Foundation Trust PALS Department on 01865 221473*) or the Head of the University of Oxford Clinical Trials and Research Governance office (01865 616480/ e-mail: ctrg@admin.ox.ac.uk).

The University of Oxford, as Sponsor, has appropriate insurance in place in the unlikely event that you suffer any harm as a direct consequence of your participation in this trial. NHS indemnity operates in respect of the clinical treatment which is provided.

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

Patient feedback was obtained during the development of the study protocol, from a panel coordinated by the National Institute for Healthcare Research (NIHR) Thames valley and South Midlands Clinical Research Network.

Who is organising and funding the study?

The study is being run from within the Nuffield Department of Surgical Sciences, part of the University of Oxford, based at the John Radcliffe Hospital Oxford. It has been funded by a grant from Abbott Laboratories.

Who has reviewed the study?

The study has been reviewed by the Clinical Trials and Research Governance (CTRG) department, University of Oxford.

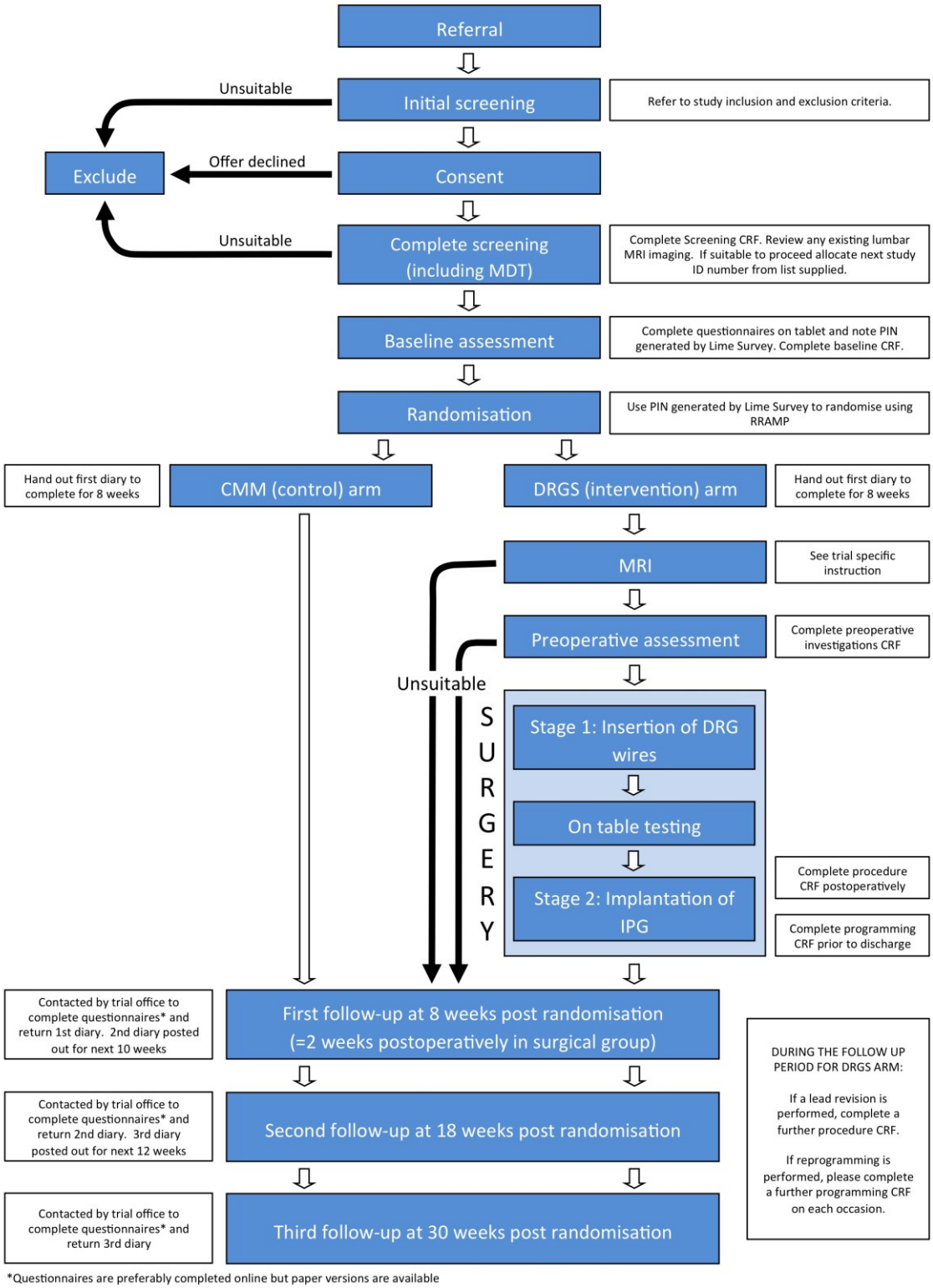
This study has been reviewed and given a favourable opinion by Oxford C Research Ethics Committee (REC).

Further information and contact details:

Please contact Professor James FitzGerald (Chief Investigator) by telephone on 01865 234605 or email james.fitzgerald@nds.ox.ac.uk (or pentagons@nds.ox.ac.uk). Full address details: Nuffield Department of Surgical Sciences, Department of Neurosurgery, West Wing, Level 3, John Radcliffe Hospital, Oxford OX3 9DU.

Thank you for considering taking part.

Study flowchart



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