[Trust letterhead/logo]

OPTION-DM Trial:

Optimal **P**athway for **T**reat**I**ng neur**O**pathic pai**N** in **D**iabetes **M**ellitus

Participant Information Sheet

We would like to invite you to take part in the OPTION-DM research study which is being organised by Sheffield Teaching Hospitals and the University of Sheffield. Before you decide if you would like to take part, we would like to explain why the research is being done and what it would involve for you.

Please take time to read the following information carefully. Talk to family, friends or health professionals about the study if you wish. Please ask us if there is anything that is not clear or if you would like more information. Whether you join the study is entirely up to you.

How to contact us:
If you have any questions about this study, please contact:

<insert local contact details>

Contents

1. What is the purpose of this research?..... p1
2. Why have I been invited to take part?..... p2
3. How is this research carried out?..... p2
4. What will happen to me if I agree to take part?..... p3
5. What are the possible benefits and drawbacks of taking part?..... p4
6. What else do I need to know?..... p5
7. Additional research..... p6
8. Further information and contact details..... P7

1. What is the purpose of this research?

The number of people with diabetes is growing rapidly in the UK. Unfortunately, diabetes causes nerve damage that in turn can cause painful symptoms in the feet, legs and hands. One quarter of all people with diabetes experience these symptoms, known as “painful diabetic neuropathy”. Currently, the recommended treatment in the UK is a choice of four medications; amitriptyline, duloxetine, pregabalin or gabapentin. If initial treatment with one of these drugs is not fully effective, it is recommended that one of the other medications is added in combination with the first.

Until now, these medications, and their combinations, have not been systematically compared against each other to see which is best. We want to find out which is the most effective initial treatment and then the best combination treatment for patients with painful diabetic neuropathy. We will do this by comparing three different treatment pathways using amitriptyline, duloxetine and pregabalin, and their combinations. Please note that gabapentin will not be used in this study.

At the moment we don't know which is the best initial treatment, or combination of treatments, for painful diabetic neuropathy. This study will provide important information about the most effective treatments which will inform the treatment of future patients.

2. Why have I been invited to take part?

You are being invited to take part in this study because you have painful diabetic neuropathy. We are planning to include approximately 400 patients across the country.

Do I have to take part?
No. It is up to you to decide whether or not to join the study. This information sheet describes the study and a member of the research team will talk it through with you and answer any questions you may have. If you agree to take part, we will give you this information sheet to keep and we will then ask you to sign a consent form. You are still free to withdraw at any time, without giving a reason. Whatever you decide, this will not affect the standard of care you receive.

3. How is this research carried out?

This study will look at 3 treatment pathways:

Pathway 1: Amitriptyline (with the addition of pregabalin if needed)
Pathway 2: Duloxetine (with the addition of pregabalin if needed)
Pathway 3: Pregabalin (with the addition of amitriptyline if needed)

Each patient in the study will receive all 3 treatment pathways but the order in which you receive them will be decided at random.

Who decides which order I will receive the treatments in?
A computer program will randomly decide the order that you receive the treatment pathways. You will receive all the treatment pathways, regardless of which order you are allocated to.

At the moment, we don't know which treatment works best for patients. Randomly allocating the order of the treatments will help us to compare the different treatments in an equal way.

Neither you, nor the local study team, will know which treatment order you have been allocated to. All the medications in the study will look the same. You will always receive the active treatment in each pathway but sometimes you will also be given a placebo. We use a placebo so that you always take the same number of tablets at each time point, regardless of which treatment you are on. A placebo tablet looks exactly like the active treatment but does not contain any medicine. This helps us compare the treatments fairly. If necessary, your doctor will be able to find out which treatment you are taking at any point during the study.

4. What will happen to me if I agree to take part?

Before you start study treatment:

If you agree to take part, we will need to make sure that the study is right for you. At your first visit, a member of the study team will answer any questions that you may have, and will ask you to sign an informed consent form. They will then examine you, and ask some questions about your medical history. A blood test and a heart tracing (ECG) will be done and you will undergo a standard sensory examination. This examination includes assessment of sensory symptoms, examination of the feet (by evaluation of pin-prick, temperature, light touch, position senses and vibration sensations) and examination of knee and ankle reflexes. In addition a light brush stroke will be applied to the feet to see how this is felt.

Before you start the study treatment, you will be asked to slowly reduce the dose of any current pain medications over the course of 1 week. You will then have a one week 'washout' period, where you do not take any prescribed pain medication. Please note that you can still take paracetamol up to 4 times a day if required. During this period, you will be asked to rate your pain daily on a scale from 0-10, and how much paracetamol you have used.

After the washout period, you will be asked to come back to clinic for a second visit with the study team. During this visit, we will check that the study is still right for you by looking at the pain diaries that you have completed. You will also be asked to complete some questionnaires about the pain you experience, your mood, sleep and your general health.

During study treatment:

You will be given a supply of the first treatment in your allocated pathway. You will take this first medication morning and evening for six weeks, and the dose may be increased during this time to provide effective pain relief. You will be asked to rate your pain each day to see how the study treatment is working.

At the end of the six weeks, if this medication is providing effective pain relief then you will continue taking it for another 10 weeks. However, if this medication alone is not providing effective pain relief then another medication will be added. The two medications will be taken in combination for a further ten weeks. You will be asked to continue to rate your pain each day during this period to see how the study treatment is working.

The study nurse will contact you by phone at least once a week while you are taking part in the study. This is to review the dose of your study medication, to check if there are any problems and to answer any questions.

After the first treatment pathway has finished, you will reduce your dose of this medication over one week until it is stopped completely, before starting the next pathway. This will happen in the same way as the first pathway, until you have completed all three separate treatment pathways. Each pathway will take around 4 months to complete and it will take around one year to complete all three pathways.

Figure 1 below, shows in detail what will happen at each visit during your participation in the study. This cycle of visits will take place for all three treatment pathways. Once you reach visit 8 on one pathway, you will start again at visit 2 for the second pathway, and again for the third pathway.

Are there any expenses or payments involved?

Where required participants can be reimbursed reasonable travel expenses for each appointment relating to this study.

Figure 1: Visit timelines during each treatment pathway

Visit 1 - 90 Minutes	•Confirm suitability & take consent •Medical history, physical examination, blood test & ECG •Daily pain rating instructions given out •Reduce current pain medication over one week followed by one week washout period
Visit 2 - 60 minutes Week 0 (Study Entry)	•Clinical assessments •Neuropathic pain assessment •Patient completed questionnaires •Study medication dispensed
Visit 3 - 30 minutes Week 2	•Medication review (dose amended if necessary) •Study medication dispensed
Visit 4 - 30 minutes Week 3	•Medication review (dose amended if necessary) •Study medication dispensed
Visit 5 - 45 minutes Week 6	•Decision to either continue on the first medication alone, or add the second medication (based on pain diaries over the last 7 days) •Study medication dispensed
Visit 6 - 30 minutes Week 8	•Visit 6 only required if second medication has been started •Medication review (dose of second medication amended if necessary) •Study medication dispensed
Visit 7 - 30 minutes Week 9	•Medication review (dose of second medication amended if necessary) •Study medication dispensed
Visit 8 - 30 minutes Week 16	•Clinical assessments •Neuropathic pain assessment •Patient completed questionnaires •Instructions on reducing current medication(s) ready for starting the next pathway

5. What are the possible benefits and drawbacks of taking part?

What are the possible benefits?

You will receive proper health care whether you choose to participate in the study or not. We do not know which medication will be better for you and this is the reason for carrying out this research. If one medication is found to be more effective than the others, this will inform the treatment of future patients with painful diabetic neuropathy. By taking part in this study you will be directly helping us to do this.

You will be contacted weekly by the study nurse during the study so you will receive more follow-up care than normal. You will also be given a phone number for the study team in case of questions or concerns.

You may find a treatment pathway that is effective in treating your painful diabetic neuropathy. When the trial is finished, approximately August 2019, we will let you know in which order you received the treatments. You will then be able to request your preferred treatment from your care team. Unfortunately it is not possible for us to let you know which treatment you are on before the trial has finished as this may affect the results. If you have any concerns about this, please discuss them with the study team.

What are the possible drawbacks?

All three of the medications we are using in this research have been approved for use in patients with diabetic painful neuropathy. They are all considered safe treatments.

You will need to stop your current pain medication before starting the study and between each pathway you will need to stop taking the study medication. Discontinuation of study medication may result in temporary withdrawal side effects such as anxiety or an increase in pain. This will be minimised by reducing the dose of your medication for 3 days before the medications are completely stopped. The amount of time without any treatment will be short but if you have concerns about this please discuss them with the study team.

Taking part in this research may mean additional appointments at the hospital, compared to the number of appointments you receive normally. Although this means extra travel, you will be reimbursed for your travel costs in attending these hospital appointments if required.

What are the side effects of any treatment received when taking part?

Some participants may experience side effects with the study medications.

Very common side effects (may affect more than 1 in 10 people) include: headaches, feeling sleepy, dry mouth and eyes, feeling sick, and dizziness.

Common side effects (may affect up to 1 in 10 people) include: constipation, change in appetite, slight weight gain, blurred vision, problems passing urine, changes in sexual functioning, swelling of the body including extremities and fatigue.

Rare side effects (may affect up to 1 in 1000 people) include: serious allergic reactions and increased risk of suicidal behaviour. Although these are rare, if you become concerned, please contact your study team.

It is also possible that other side effects could occur. We will be monitoring you closely for the presence of side effects. If necessary we will alter the study medications to minimise any side effects.

Please inform your doctor or study nurse about all medical issues or symptoms that occur during this study. If you are worried at any point during the trial, you can contact your local study team for advice.

6. What else do I need to know?

Other medicines

You can still take paracetamol up to four times a day if needed, but you shouldn't take any other treatment for your neuropathic pain. If you have concerns about this, at any point in the study, you should contact the study team. Likewise, please inform the study team if you have been given or taken pain medication for other conditions during the course of the study.

You will be able to keep taking any other medications that you currently take, but please make sure you tell the study team about them before you join the trial. After starting study treatment, it is important that any doctor prescribing you with medication is aware that you are on the study. You will be given a card with details about the study which you can share with them. If you do have any changes to your regular medications during the trial, please make sure you tell the study team. Here is a list of medications that would affect your participation in the study:

- Opioid pain relieving drugs
- Capsaicin cream/high dose capsaicin patches
- Lidocaine patches
- Anti-inflammatory medications (e.g. ibupofen, diclofenac, colecoxib, etc)
- Other medications taken for epilepsy (e.g. phenytoin, carbamazepine, etc)
- Other medications taken for depression (e.g. dosulepin, imipramine, seroxat etc)
- Other neuropathic pain medications (e.g. venlafaxine, IV lignocaine etc.)

Please do not hesitate to contact the study team if there is any doubt or if you have any questions.

Pregnancy

If there is a possibility that you could become pregnant, you must use an effective contraceptive during the course of this study. If you become pregnant, or decide you want to during the study, please inform the study team as soon as possible as there are risks associated with taking the study medications during pregnancy.

Driving

Some of the study medications may affect your ability to drive. Make sure you only drive if you feel safe to do so.

Will my taking part in the study be kept confidential?

If you decide to take part, we will inform your GP. All information that is collected about you during the course of this study will be kept strictly confidential and will be held securely in line with the Data Protection Act. Investigations and/or assessments performed as part of this study may return results which may require further follow-up. If we have any concerns about your health then you will be made aware and with your agreement, your GP will be informed and a referral may be made to a medical team who can help with the problem.

With your permission, we will store your contact details (telephone number, name, email address, address) in a secure database hosted by the University of Sheffield. The database complies with the Data Protection Act and uses industry standard techniques to provide security. Your contact details will allow us to contact you about your questionnaires and with any news about the study. An anonymised copy of the computer file (with any details that might identify you removed) will be retained and may be made available to other researchers for

use in future studies. Only authorised persons such as researchers from the University of Sheffield and regulatory authorities will have access to view data that can identify you. Some documents (e.g. consent form) will be sent by post to the University of Sheffield.

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

You can stop the study at any time, you do not have to give a reason and this will not impact on the medical care you receive as part of your usual treatment. If you do decide that you no longer want to take part, please let your doctor or nurse know. We will keep any information collected up until the point that you stop taking part.

What will happen to the results of the research study?

The results of this study will be published in scientific journals and presented at scientific meetings. The findings will also be fed back to you directly by your local study team. We will also make the results available to patients through patient organisations, health information websites that are open to the public and the media.

What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak to the study team who will do their best to answer your questions (contact details below). If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure. Details can be obtained from your local Trust. In the event that something does go wrong and you are harmed during the research and this is due to someone's negligence then you may have grounds for a legal action for compensation against Sheffield Teaching Hospitals NHS Foundation Trust but you may have to pay your legal costs.
The normal National Health Service complaints mechanisms will still be available to you [local PALS details].

Who is organising and funding the research?

The study has been designed by diabetes and pain specialists and researchers. The research is organised by the University of Sheffield on behalf of Sheffield Teaching Hospitals NHS Foundation Trust (the Sponsor). The sponsor will pay your NHS Trust for including you in this study. The research is funded by the National Institute for Health Research, Health Technology Assessment (NIHR HTA) Programme (project number 15/35/03).

Who has reviewed the study?

All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee to protect your safety, rights, wellbeing and dignity. This study has been reviewed and given a favourable opinion by a Research Ethics Committee.

7. Additional Research

We are also running an optional sample collection study. We will ask your permission to take a small amount of blood to be stored for future research on painful diabetic neuropathy. The future research may include genetic analysis of the samples you provide although this is unlikely to have any implications for you personally. You will not be informed of the results of any of these tests. You can decline to participate in this part of the study without this affecting your participation in the rest of the study, or your relationship with your doctor.

The extra blood sample will be taken at the same time as your other blood tests are being taken for the trial. The samples will be stored in your local hospital before being shipped to a central research laboratory in the UK. All of the samples you give will be anonymised. This means that the samples will be identified by a code

number, not your name. Any research using your donated samples would only be carried out after an independent research ethics committee has approved it.

8. Further information and contact details

If you would like any additional information about the study, or you have any questions about this information sheet, please contact your local study team using the details below:

Insert address and telephone number of PI/research nurse/site contact

If you become concerned outside of normal office hours, please use the following out of hours contact details:

Insert out of hours contact details

Patients and doctors rely increasingly on the results of clinical studies, such as OPTION-DM, to make sure they are making the right decisions about treatment. Thank you for taking the time to read this information sheet, we hope that it has been helpful in enabling you to decide if you would like to participate in the OPTION-DM study.

This information sheet is for you to keep.