The University Of Sheffield.

Sheffield Teaching Hospitals NHS Foundation Trust

OPTION-DM

A multicentre, double-blind, centre-stratified multi-period crossover trial to evaluate the efficacy of the Optimal Pathway for TreatIng neurOpathic paiN in Diabetes Mellitus (OPTION-DM).

OPTION-DM

RESEARCH PROTOCOL
Version 12.0, 19th August 2020

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Authorised by:	Professor Solomon Tesfaye Chief Investigator

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Sheffield Clinical Trials Research Unit (CTRU)

Optimal **P**athway for **T**reat**I**ng neur**O**pathic pai**N** in **D**iabetes **M**ellitus (OPTION-DM) trial.

This document describes a clinical study, and provides information about procedures for entering participants. The protocol is not intended for use as a guide to the treatment of other participants. Amendments may be necessary; these will be circulated to known participants in the study.

Abbreviations

AE	Adverse Event
AR	Adverse Reaction
CI	Chief Investigator
CRF	Case Report Form
CTA	Clinical Trial Authorisation
CTRU	Clinical Trials Research Unit
DMEC	Data Monitoring and Ethics Committee
DMP	Data Management Plan
DPA	Data Protection Act
DPNP	Diabetic Peripheral Neuropathic Pain
EudraCT	European Union Drug Regulatory Agency Clinical Trial
GCP	Good Clinical Practice
HbA1c	Glycosylated haemoglobin
HRA	Health Research Authority
IMP	Investigational Medicinal Product
ITT	Intention to Treat
MHRA	Medicines and Healthcare products Regulatory Agency
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NRS	Numeric Rating Scale
PI	Principal Investigator
QALY	Quality Adjusted Life Years
QoL	Quality of Life
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
STH	Sheffield Teaching Hospitals
SUSAR	Suspected Unexpected Serious Adverse Reaction
mTCSS	modified Toronto Clinical Neuropathy Score
TC	Treating Clinician
TMG	Trial Management Group
TSC	Trial Steering Committee

1. Project Details

1.1 Investigator Details

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1.4 Committees

Trial Steering Committee:

Professor Andrew Rice (Chair)	Professor of Pain Research, Imperial College London
Professor Nanna Finnerup	Professor of Pain Medicine, Aarhus University
Professor Ralf Baron	Professor of Pain Research, University Medical Centre Schleswig-Holstein
Mr Arthur Durrant	Patient Research Ambassador , Sheffield Teaching Hospitals
Miss Sarah Brown	Principal Statistician, University of Leeds
Professor Roger Knaggs	Associate Professor in Clinical Pharmacy Practice
Dr Jane Lewis	Senior Lecturer in Podiatry, Cardiff School of Sport and Healthcare Science

Data Monitoring and Ethics Committee:

Professor Troels Jensen (Chair)	Director of International Diabetic Neuropathy, Aarhus University Hospital
Doctor Zoë Hoare	Principal Statistician, Bangor University

Doctor Martin Rutter	Senior Lecturer and Honorary Consultant, Manchester Diabetes Centre

1.5 Participating Centres

Sheffield Teaching Hospitals NHS Foundation Trust
Nottingham University Hospitals NHS Trust
Tameside Hospital NHS Foundation Trust
Ipswich Hospital NHS Trust
Kings College Hospital NHS Foundation Trust
Lancashire Teaching Hospitals NHS Foundation Trust
Birmingham Heartlands NHS Foundation Trust
Countess of Chester Hospital NHS Foundation Trust
Harrogate and District NHS Foundation Trust
Royal Liverpool and Broadgreen University Hospitals NHS Trust
Aintree University Hospital NHS Foundation Trust
Ninewells Hospital, NHS Tayside
Hairmyres Hospital, NHS Lanarkshire
Monklands Hospital, NHS Lanarkshire
Lancashire Care NHS Trust
Royal Wolverhampton NHS Trust
Gateshead Health NHS Foundation trust
Morriston Hospital, Abertawe Bro Morgannwg University Local Health Board

1.6 Role of the Funder

The funder has reviewed the research protocol but will have no role in data collection, analysis, data interpretation, report writing or in the decision to submit the report for publication.

1.7 Protocol amendments

Protocol amendments from version 11.0 to version 12.0

Section 9.8

- End of trial definition updated to allow sample analyses to be completed.

Protocol amendments from version 10.0 to version 11.0

Section 1.8

- Sample size and study end date amended.

Section 6.3

- Exclusion criterion 7 updated to clarify that patients who are taking concomitant citalopram at baseline are not eligible for the study.
- Exclusion criterion 12 updated to exclude patients with second or third degree heart block or left bundle branch block (patients with right bundle branch block or first degree heart block may be included following discussion with cardiology team).

Section 11.3

- Amended to include information on the updated sample size for the study.

Section 16

- NIHR disclaimer added.

Protocol amendments form version 9.0 to version 10.0

Section 1.4

- TSC membership list updated to reflect recent changes.

Section 6.2

- Inclusion criterion 3 updated to clarify that at least 4 questions must be answered as 'yes' on the DN4 for the patient to be eligible.
- Inclusion criterion 6 updated to allow patients to be randomised early if their pain scores are high, provided the mean pain score for the week is above 4.

Section 6.3

- Exclusion criterion 11 updated to exclude patients with heart failure NYHA class III or above.
- Exclusion criterion 14 updated to clarify the exclusion requirements for postural hypotension and to allow investigator discretion to be used.

Section 6.5

- Updated to allow a delay between screening and starting the washout/baseline weeks provided the randomisation visit is scheduled no more than 4 weeks after screening.

Section 6.5.1

- Updated to clarify that both AST and ALT are required for the liver function tests.
- Added ankle brachial pressure index recording for patients with active foot ulcers, unless the pulse is palpable.

Section 6.5.3

- Updated to allow the randomisation visit to be brought forward for patients with high pain scores. Randomisation can be completed as soon as the mean pain score for the week is at least 4.

Section 8

- Clarification added regarding the requirements for prescription completion and sign off.
- Changes throughout this section to clarify the treatment decisions process.

Section 8.10

- Updated to potentially allow short term use of prohibited concomitant treatments. Individual cases to be discussed with CTRU.

Section 9.1

- Updated to confirm that ALT and AST are required for the liver function tests
- Updated to clarify that if a participant has postural hypotension at week 16 of a pathway, this should be repeated at week 0 of the next pathway.

Section 10.2

- Updated to clarify that episodes of severe hypoglycaemia and diabetic ketoacidosis only need to be reported as SAEs if they meet the definition of serious provided in table 6.

Protocol amendments form version 8.0 to version 9.0

Section 8.3.4

- Updated to allow the study medication to be tapered more gradually between pathways if needed at the discretion of the investigator.

Protocol amendments from version 7.0 to version 8.0

Section 6.3

- Exclusion criterion 7 updated to allow participants with prior concomitant and safe use of selective serotonin reuptake inhibitors (SSRIs) with study medication (duloxetine and/or amitriptyline) to join the study.
- Exclusion criterion 21 updated to clarify that patients with active foot ulcers are eligible for the study unless the investigator feels that the ulcer will have a confounding or detrimental effect on the primary outcome or patient participation.

Section 6.5.2

- Updated to allow duloxetine to be tapered over a period of up to 2 weeks during the initial washout period.

Section 8.10

- Updated to clarify the requirements for including participants taking concomitant SSRIs.

Protocol amendments from version 6.0 to version 7.0

Figure 3

- Updated to clarify that week 1 and week 7 procedures can be completed over the phone or face to face at a study visit.

Section 6.1

- Updated to include details regarding the recruitment processes in Scotland.

Section 6.2

- Inclusion criterion 2 updated to clarify that neuropathic pain may be present in the hands.

Section 6.3

- Exclusion criterion 1 updated to clarify that only non-diabetic symmetrical poly neuropathies are excluded from the trial.
- Exclusion criterion 9 updated to clarify which liver function tests are relevant for trial eligibility.
- Exclusion criterion 12 updated to include current history of arrhythmia is also an exclusion for the trial.

Section 6.5.2

- Updated to allow investigator discretion for the washout period prior to the baseline period. The washout can be between 1 and 4 days as required.
- Updated to clarify that patients who are not taking any neuropathic pain medication at screening do not need to go through the washout period.
- Updated to clarify that no additional washout time is required for participants who have been tapered off opiates over a period of 2 weeks.

Section 6.5.4

- Updated to allow participants to begin study treatment on the day of randomisation or the following morning.

Section 8.2

- Updated to clarify that participant preference is taken into account when making dose titration decisions.

Sections 8.3.1 and 8.3.2

- Updated to allow a visit, rather than a telephone call, at weeks 1 and week 7 where necessary.

Section 8.10

- List of prohibited medications updated to include opsite patches.

Section 9.1

- Footnote C updated to clarify that if a visit cannot be performed within +/- 2 days of the scheduled visit date, CTRU must be contacted for advice.

Protocol amendments from version 5.0 to version 6.0

Section 1.5

- List of participating centres updated.

Figure 2

- Amended to highlight the different dosing and titration schedules for patients with eGFR 30-59ml/min.

Figure 3

- Amended to clarify that blood tests are required at week 16.

Section 5.2

- Updated to clarify that if a participant withdraws from the study, any blood samples already collected will be kept unless the participant requests otherwise.

Section 6.1

- Updated to clarify the pre-screening procedures.

Section 6.5.1

- Updated to clarify that details of previous medications will be collected at the screening visit.

Section 6.5.4

- Updated to clarify that the pain catastrophizing scale is required at the randomisation visit.

Sections 6.5.2, 6.5.4 and 9.1

- Details added regarding text message data collection for pain scores.

Sections 8.1, 8.2 and 8.7

- Updated to clarify that there are 2 dosing schedules for pregabalin which are based on the participant's latest eGFR result.

Section 8.3.1

- Updated to clarify that second line treatment can be started later than week 6 if a participant becomes a non-responder during the second treatment phase.

Section 8.9.2

- Updated to clarify the unblinding process for safety reporting.

Section 9.1

- Pain diaries added to list of assessments at week -2.
- Footnote 'h' updated to clarify that the blood sample for future research can be obtained at the same time as any other study blood sample.
- Footnote 'j' updated to include details regarding text message data collection for pain scores.
- Adverse events and compliance assessment added to the list of assessments at week 0. Footnote 'l' added to clarify that these assessments are not required at week 0 of pathway 1 (randomisation visit).

Section 13 & 14

- Updated to clarify the requirements for source data and the process for validating data within the Prospect database.

Protocol amendments from version 4.0 to version 5.0

Section 6.5.1:

- Serum creatinine added to list of assessments at week -2.

Section 6.5.4:

- Pregnancy test added to list of assessments at randomisation visit for women of child bearing potential.

Section 8.9.1:

- Updated to clarify the process for emergency unblinding during office hours.

Section 8.11:

- Updated to clarify the methods of contraception which are acceptable within the trial.

Section 9.1:

- Pregnancy testing added to the schedule of assessments.

- Serum creatinine added to the list of blood tests required.

Protocol amendments from version 3.0 to version 4.0

Section1.4:

- TSC membership updated.

Figure 2:

- Typographical error in second line treatment maintenance phase duration corrected.

Section 8.2:

- Updated to clarify that a dose review is only required for severe or intolerable side effects.

Section 8.9.1:

- Responsibility for emergency unblinding out of hours updated to allow for variation across centres.

Section 9.1:

- Informed consent added to list of procedures for clarity.
- Schedule of assessments updated to clarify that the patient completed questionnaires are only required at the randomisation visit, not week 0 of every pathway.
- Typographical error on footnotes corrected.

Sections 9.4, 9.5 and 9.6

- Minor updates made for clarification on timing of assessments and process for completing questionnaires.

Protocol amendments from version 2.0 to version 3.0

Section 4.4:

- Scoring system updated for RAND SF-36.
- HADs endpoints updated.
- New patient perceived tolerability endpoints added.

Section 5.2:

- Updated to clarify that blood samples may be shipped directly to the central lab or stored locally prior to shipping.

Section 6.2:

- Inclusion criterion 2 amended for clarification.
- Inclusion criterion 3 amended – the modified Toronto Clinical Neuropathy Score will be used.
- Inclusion criterion 4 amended for clarification.

Section 6.3:

- Exclusion criteria 2, 3, 8 and 15 amended for clarification.
- Exclusion criterion 13 amended for safety reasons – patients with recent myocardial infarction to be excluded.

- Exclusion criteria added for major amputations of the lower limbs and active diabetic foot ulcers.

Section 6.5.1: Vital signs assessment moved from week 0 to week -2.

Section 6.5.2: Guidance regarding taper doses for participants taking morphine equivalent at screening visit.

Section 8.3.4: Details of taper doses added.

Section 8.9.1: Clarification added that the on-call pharmacist at each centre will be responsible for emergency unblinding out of hours.

Section 8.11: Clarification added with regards to reporting requirements for pregnancy including obtaining informed consent for follow up.

Section 9.1: Schedule of assessments updated to include the mTCNS and tolerability scale.

Section 10.4.1: Clarification that events classed as serious, but where the causality cannot be assessed, will be treated as 'related' until the relationship can be assessed.

In addition to the above, minor typographical errors were corrected throughout protocol and wording updated for consistency across trial documentation. Please refer to OPTION-DM Document Changes, Substantial Amendment 1 for full details.

Protocol amendments from version 1.0 to version 2.0
Page 21: Paragraph added to clarify procedures to be followed in the event that a participant demonstrates suicidal ideation.

1.8 Study Summary

Study Title:	Optimal Pathway for Treating neurOpathIc paiN in Diabetes Mellitus (OPTION-DM)
EudraCT:	2016-003146-89
Sponsor:	Sheffield Teaching Hospitals
Funder:	NIHR HTA (project number 15/35/03)
Project start date:	1st June 2016
Project end date:	31st January 2021
Study Design:	Multicentre, double-blind, 3x3 Williams Square crossover trial.
Participants:	152 participants with Diabetic Peripheral Neuropathic Pain (DPNP).
Setting:	Participants will be recruited from 8 secondary care DPNP centres and 80 primary care practices.
Interventions:	OPTION-DM will study 3 treatment pathways: • Amitriptyline supplemented with pregabalin (A-P Pathway) • Duloxetine supplemented with pregabalin (D-P Pathway) • Pregabalin supplemented with amitriptyline (P-A Pathway) Each treatment pathway has 2 treatment periods: 6 weeks monotherapy followed by 10 weeks combination therapy. Those

<table>
<tr><td></td><td>patients who have adequate pain relief after 6 weeks will remain on monotherapy for the second treatment period. Each treatment pathway is preceded by a one week washout period. Refer to Figure 1 for details</td></tr>
<tr><td>Dose Titration</td><td>There will be 3 dose levels for each drug. Participants will start on the lowest dose level of each drug and the dose will be titrated up to a maximum tolerated dose over the first 2 weeks of treatment. Refer to Figure 2 for details.</td></tr>
<tr><td>Randomisation:</td><td>All participants will receive all three treatment pathways. Randomisation will determine the order in which they receive the treatment pathways. Participants will be allocated to one of 6 sequences in an equal allocation to sequences (1:1:1:1:1:1):
<table>
<tr><th></th><th>Treatment Pathway 1</th><th>Treatment Pathway 2</th><th>Treatment Pathway 3</th></tr>
<tr><td>Sequence 1</td><td>A-P</td><td>D-P</td><td>P-A</td></tr>
<tr><td>Sequence 2</td><td>A-P</td><td>P-A</td><td>D-P</td></tr>
<tr><td>Sequence 3</td><td>D-P</td><td>A-P</td><td>P-A</td></tr>
<tr><td>Sequence 4</td><td>D-P</td><td>P-A</td><td>A-P</td></tr>
<tr><td>Sequence 5</td><td>P-A</td><td>A-P</td><td>D-P</td></tr>
<tr><td>Sequence 6</td><td>P-A</td><td>D-P</td><td>A-P</td></tr>
</table></td></tr>
<tr><td>Duration:</td><td>Participants will be recruited over one year and each participant will remain in the study for around one year.</td></tr>
<tr><td>Hypothesis:</td><td>The null hypothesis is that there is no difference between the treatment pathways and the alternative hypothesis is that there is a true difference.</td></tr>
<tr><td>Primary Objective:</td><td>To identify the most clinically beneficial treatment pathway for DPNP</td></tr>
<tr><td>Secondary Objectives:</td><td>- To identify differences in :
• Other clinically important benefits (pain interference with function, mood, health status, sleep duration and quality, responder rates analysis [30% and 50% pain relief], Patient Global Impression of Change[PGIC])
• Cost-effectiveness
• Tolerability
- To identify the most clinically beneficial, cost effective and best tolerated monotherapy at week 6.
- To conduct a subgroup study to investigate if patient phenotypes predict response to treatment.</td></tr>
</table>

Figure 1: Patient flow chart. Visits from week 0 to week 16 are repeated until all three pathways have been completed.

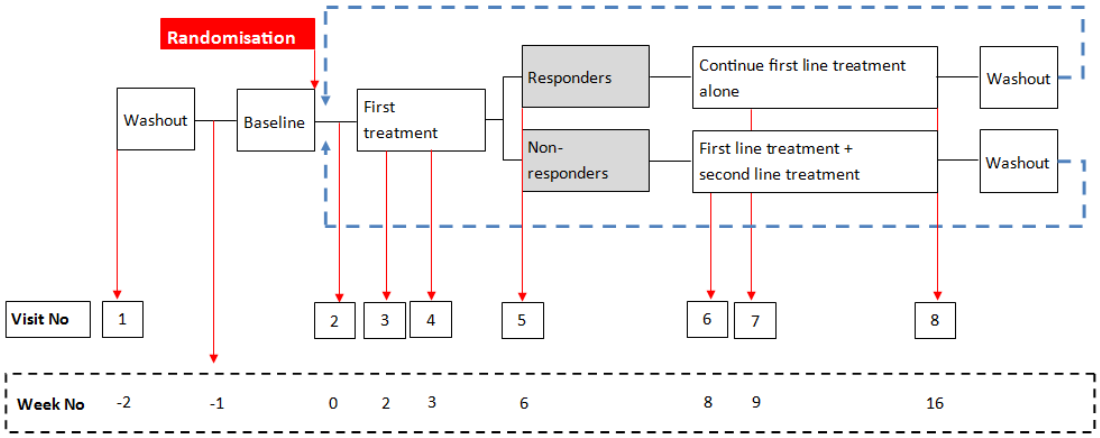

Randomisation
Washout
Baseline
First treatment
Responders
Non-responders
Continue first line treatment alone
First line treatment + second line treatment
Washout
Washout
Visit No
1
2
3
4
5
6
7
8
Week No
-2
-1
0
2
3
6
8
9
16

Figure 2a: Dosing and titration schedule for each treatment pathway (**standard pregabalin dosing, eGFR ≥60ml/min**). Participants continue on maintenance dose of drug from the First Treatment Phase for the duration of the Second Treatment Phase.

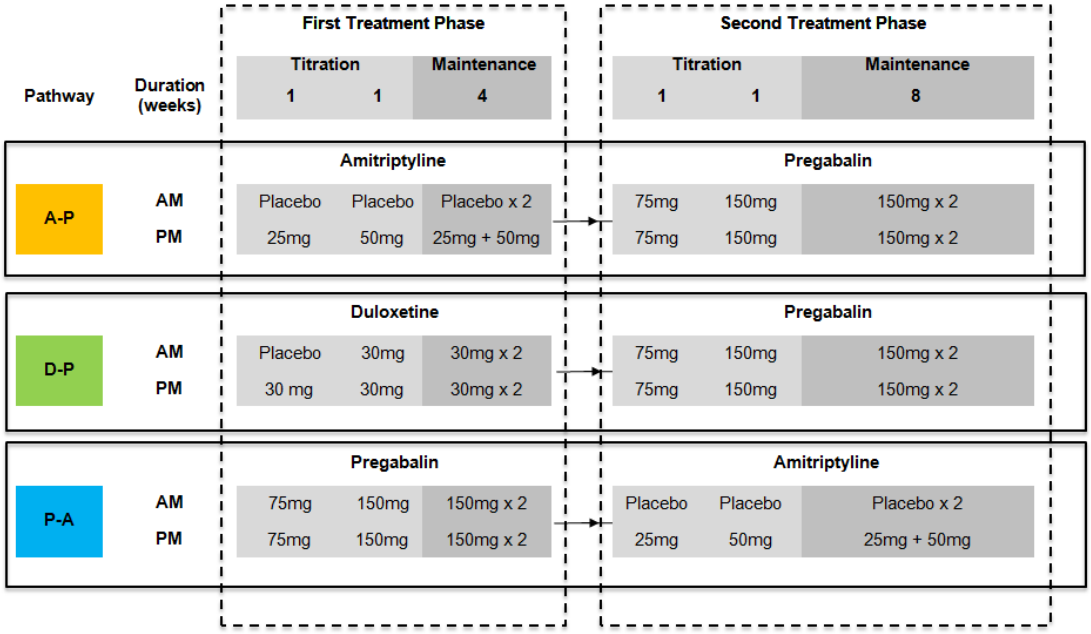


Figure 2b: Dosing and titration schedule for each treatment pathway (**reduced pregabalin dosing, eGFR 30-59ml/min**). Participants continue on maintenance dose of drug from the First Treatment Phase for the duration of the Second Treatment Phase.

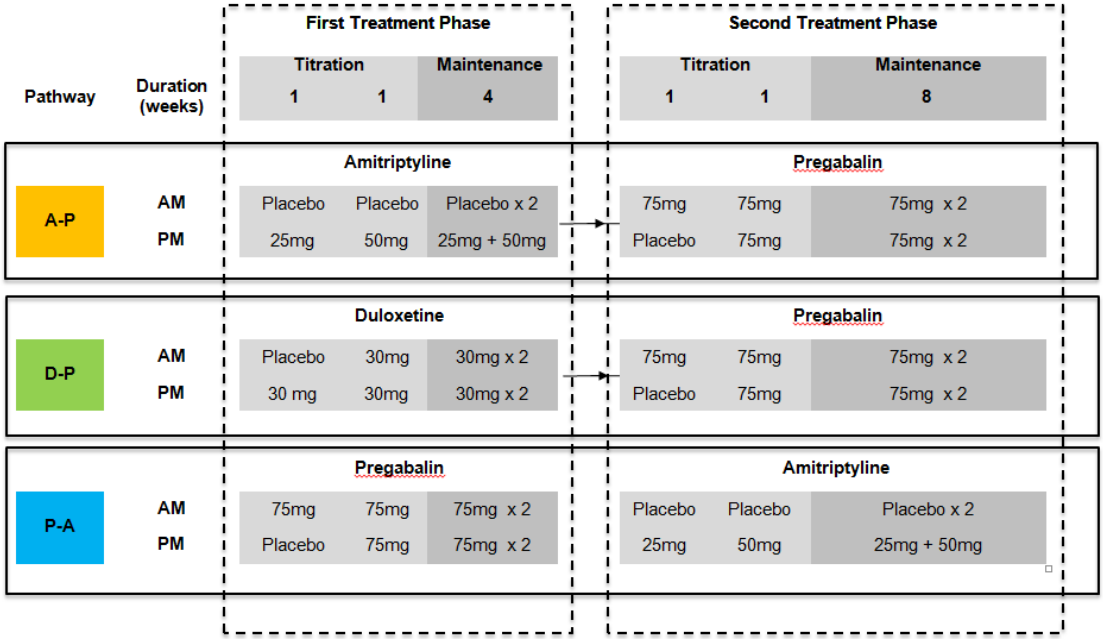


Figure 3: Patient visits during each pathway.

2. Introduction

In August 2015 Diabetes UK announced that the prevalence of diabetes had increased by 60% over the previous decade to 3.3 million. Diabetic peripheral neuropathic pain (DPNP) is a serious complication affecting up to 20-26% of these patients (1,2). With the prevalence of diabetes set to increase by epidemic proportions over the next decade, DPNP will pose a major treatment challenge (3,4).

DPNP causes burning, deep aching, “electric shock” like, lancinating (also likened as “stabbing or knife like” pains); contact pain often with day-time clothes and bedclothes (allodynia); 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 (4). 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 (2,5) and causes insomnia, poor Quality of Life (QoL), unemployment, and depression (6–9).

The mainstay of treatment for DPNP is pharmacotherapy. Recent NICE guidance (173)(10) recommends a choice of amitriptyline, duloxetine, pregabalin or gabapentin as initial treatment. All are licensed treatments for DPNP except amitriptyline, which has been used off-license for more than 25 years. There is moderate evidence for the efficacy of each drug based on Cochrane reviews (11–14) and meta-analyses (15–17), but the best we can hope for any monotherapy is 50% pain relief in 50% of patients (10). This is often accompanied by side effects (dry mouth, constipation, sedation, dizziness, falls, nausea, oedema etc.) in around 10-20% depending on dose. NICE recommends combination treatment if initial treatment is not effective (the majority) (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 flawed with inadequate power, inappropriate end-points, short duration of follow-up and 3) many RCTs lacked appropriate HR-QoL measures including functionality and failed to measure impact of drug-related adverse effects on health economics and QoL (10). An RCT is needed to address these deficiencies.

The OPTION-DM study will be a multicentre, double-blind, 3x3 Williams Square crossover study of Treatment Pathways to evaluate the superiority of at least one Pathway (amitriptyline supplemented with pregabalin, duloxetine supplemented with pregabalin and pregabalin supplemented with amitriptyline) in reducing the 7-day average 24-hour pain in patients with DPNP.

Eligible patients will be randomised to one of six treatment sequences. Each sequence will examine all three Treatment Pathways in stratified order. Each Treatment Pathway will consist of two periods (6-week monotherapy followed by 10-week combination therapy). An internal pilot will be incorporated to assess the feasibility of recruitment and retention. An economic analysis alongside this study will be used to determine the cost-effectiveness of each Treatment Pathway.

2.2 Why is this research needed now?

Recent Cochrane reviews (11–14), meta-analyses (15–17), consensus guidelines (18–20) and NICE 173 (10) support the choice of amitriptyline (25-75mg/day), duloxetine (60-120mg/day) and the α-2-δagonists pregabalin (300-600mg/day) and gabapentin (0.9-3.6g/day) as first line agents for DPNP. However, these recommendations are not based on solid evidence.

Comparator studies

Two small randomized, double-blind, cross-over, short duration (5 week follow-up) studies compared amitriptyline with pregabalin (n=51) (21), and amitriptyline with duloxetine (n=58) (22) in DPNP. The studies were underpowered to detect any differences in pain relief between the drugs. Another underpowered, and short (4 weeks) RCT compared amitriptyline (n=27), duloxetine (n=28) and pregabalin (n=28) (23) and found no differences between the groups. The lack of head-to-head studies led to an indirect comparison of the efficacy and tolerability of duloxetine with pregabalin using placebo as a common comparator, but found no difference in 24-hour pain severity between the two (24).

Combination studies

Low-dose combination of gabapentin and morphine was more effective than higher doses of either (25) although curiously there was no difference between placebo and gabapentin (26). Finally, the COMBO-DN study (27), which is the largest combination study in DPNP (n=804), assessed whether combining standard doses of duloxetine (60mg/day) and pregabalin (300mg/day) was superior to maximum doses of either. It also compared head-to-head the standard doses of duloxetin and pregabalin. The study found no difference in the change in 24-hour average pain or adverse events between standard dose combination vs. high dose monotherapy (27). Although the standard dose of duloxetine was superior to pregabalin, there was equivalent efficacy with pregabalin at higher doses (27).

Published economic evaluations

To date, there is no conclusive evidence regarding the cost-effectiveness of amitriptyline, duloxetine and pregabalin for DPNP. Wu et al. (28) conducted a cost-utility analysis of duloxetine compared to usual care as part of an open-label study extension. They conclude that duloxetine was a dominant treatment (more effective and less costly). However, methodological issues limit the generalizability of this conclusion. Beard et al. (29) developed a short-term decision tree to estimate alternative treatment sequences that include duloxetine. A standard treatment sequence was defined as amitriptyline, gabapentin and then opioid-related treatment. Duloxetine was evaluated as a first, second, third or fourth-line therapy. First-line use of duloxetine was both the most effective, and most cost-effective treatment strategy. O'Connor et al. (30) compared the costs and Quality Adjusted Life Years (QALYs) of first line desipramine, duloxetine, gabapentin and pregabalin. They conclude that desipramine and duloxetine may be more cost effective than gabapentin or pregabalin for first line treatment of DPNP. The limited published evidence highlights the need for a definitive evaluation of the costs and health benefits of alternative treatment sequences for DPNP. This would inform NHS guidance and commissioning and ensure an efficient use of limited health resources.

In summary, there is lack of head-to-head studies of current drugs and their combinations highlighting the need for carefully designed RCTs, involving patients recruited from both primary and secondary care, to identify the most cost-effective and best tolerated Treatment Pathway for DPNP.

2.3 Rationale for the Study

There are no better ways of tackling DPNP

The risk factors for DPNP are not known and can't be addressed to improve prognosis. The pathophysiology of DPNP remains poorly understood (4) and there are no agreed disease modifying treatments (31). New compounds in development, are unlikely to be better than current first line drugs(31,32). Based on the trajectory of new drug developments for DPNP over the past 25 years, the emergence and use of revolutionary new drugs that are considerably more efficacious than current ones seems unlikely in the next decade. Non-pharmacological treatments for DPNP are available but appear to be inferior to current first line drugs. There is therefore a strong case for more robust study evidence from existing drugs (10).

It has the potential to improve the physical and psychological health of patients

Currently there is considerable uncertainty regarding which first line drug to start patients on, and when this provides sub-optimal relief, which drug to add in a combination treatment. This results in inadequate pain management increasing: patient suffering (anxiety and depression) (33), disability (reduced functionality) (7), family problems (unemployment) (9) and impaired social functioning (isolation). Thus, the importance of identifying the most optimal Treatment Pathway for these needy patients cannot be overestimated.

It has the potential to benefit the NHS

There is clear evidence that increasing pain severity results in increased health care utilisation (7). In 2001 the annual costs of managing DPNP in the US ranged between $4.6-13.7 billion (34). In 2003 the likelihood of a hospital admission for DPNP patients was more than 2.5-fold higher relative to non-DPNP diabetes patients, and the estimated marginal cost per patient associated with DPNP was $5907/year (35). Thus relieving pain effectively will reduce health care utilisation benefiting the NHS. Patients are being prescribed expensive options without any cost-effectiveness data. In the past year, Sheffield CCG alone spent nearly £3.1 million on pregabalin at an average of £49.77/prescription. If these had been prescribed as amitriptyline there would be a saving of nearly £3.04 million (36). Although the pregabalin patent is due to expire in 2017 in the UK, the generic preparation will likely be more expensive than amitriptyline. There may therefore be considerable savings if the most cost effective pathway is identified for DPNP management.

In summary, this study has a potential benefit to sufferers, carers, health care professionals, the NHS and society at large.

2.4 Justification of the Study Design

Why exclude gabapentin?

There is clear rationale for not studying two α-2-δ agonists (pregabalin and gabapentin) as:

1. The evidence for gabapentin is only derived from one reasonable quality RCT (4 week titration and 4 week treatment phase) (37) compared to 8 RCTs in pregabalin and evidence supported by meta-analysis (15)
2. Gabapentin is a thrice daily drug
3. Gabapentin, unlike pregabalin doesn't have linear pharmacokinetics and requires a long titration period of up to 2 months (19) to avoid toxicity.

Why examine Treatment Pathways?

Although, a head-to-head RCT of individual drugs and a separate RCT of combination therapy could be designed, in our opinion an examination of a Treatment Pathway as a whole is the most efficient and applicable to current UK clinical practice. This is because most patients are started on monotherapy and will require a second agent added in combination within a few months. Only a very small minority will either have massive benefit from monotherapy (24-hour pain scores < 3 on a Numeric Rating Scale, NRS) and will not need another agent, or will not tolerate monotherapy (or monotherapy is completely ineffective) and will be switched to another agent. Thus, OPTION-DM, which will examine the whole Treatment Pathway, will capture more clinically relevant outcomes than artificially designed, head-to-head monotherapy or combination studies. Hence, the outcomes of this study will be readily generalisable to current UK clinical practice.

Which Treatment Pathways?

Our proposed Treatment Pathways are as follows:

1. Amitriptyline supplemented with pregabalin,
2. Pregabalin supplemented with amitriptyline,
3. Duloxetine supplemented with pregabalin.

We will not examine the pathway of pregabalin supplemented by duloxetine because of the COMBO-DN findings (27). In this study, there was no difference in pain reduction if pregabalin was added to duloxetine or vice versa (27). However, duloxetine was superior to pregabalin as an initial treatment, is a once daily preparation and is also the cheaper option in the UK. There is thus a good rational for starting patients on duloxetine and then adding pregabalin in combination. Finally, as both amitriptyline and duloxetine are antidepressants there is little rational for combining both.

Efficient design with 16-week Treatment Pathways

This will be an efficiently designed head-to-head, cross-over RCT (38) with each patient undergoing all pathways. The duration of monotherapy in each pathway is at least 6 weeks, an adequate duration to assess treatment effect and whether combination therapy is indicated (19,38). The subsequent 10-week combination therapy in patients with partial benefit from monotherapy will be adequate to assess stabilised treatment outcomes (27). The COMBO-DN study used fixed dose titration regimens regardless of treatment response. This resulted in a drop-out rate of 17% during monotherapy and 12% during combination therapy (27). However, this pragmatic RCT employing a flexible dosing regimen to achieve maximum tolerated doses, based on individual responses, we envision will reduce the drop-out rate. The use of rescue medication, frequent clinic and telephone contacts and the need for active therapy we envision will further reduce drop-out rates. Completion rates will be monitored on an ongoing basis.

3. Aims and objectives

The main aims of this study are to determine the most clinically beneficial, cost effective and tolerated Treatment Pathway for patients with DPNP.

This multi-centre study has been designed to have direct clinical applicability in the management of DPNP in the UK following completion.

3.1 Efficacy objectives

To evaluate if at least one of the three pathways is superior to the other pathways in improving:

- NRS 24-hour pain scores averaged over the last 7 days (primary efficacy objective)
- Other efficacy outcomes (defined in Section 4.4 - secondary efficacy objectives)
- Cost effectiveness outcomes (defined in Section 4.4 secondary cost effectiveness objectives)

To evaluate if at least one monotherapy is superior to a different monotherapy in improving NRS 24-hour pain scores averaged over the last 7 days (secondary efficacy objective)

3.2 Safety objectives

To describe Adverse Events and Serious Adverse Events data (summarised both at patient level and event level) and report listings between the different Treatment Pathways for DPNP.

3.4 Subgroup study objectives

To conduct a subgroup study to investigate if patient phenotypes (demography, Neuropathic Pain Symptom Inventory [NPSI], assessments of mood, sleep etc.) predict response to treatment.

4. Study Design

This will be a multicentre, double-blind, centre-stratified, multi-period crossover study with equal allocation to sequences (1:1:1:1:1:1) of Treatment Pathways with a 12 month internal pilot. Participants and the local research team will be blinded to treatment allocation with the exception of the site pharmacist who will be unblinded.

The study will evaluate the superiority of at least one Pathway in reducing the 7-day average 24-hour pain in patients with DPNP.

4.1 Feasibility Outcomes:

The study will contain a 12 month internal pilot study to assess the feasibility of recruitment and retention in the study. The TSC will review recruitment rates after 6 months of recruitment and will also review recruitment and retention rates after 12 months of recruitment. These rates will be reviewed relative to pre-specified targets agreed with the NIHR HTA. After 6 months of recruitment the Trial Steering Committee will assess recruitment and retention data and report to the NIHR on whether criteria for stopping have been met or whether the study will continue.

4.2 Primary Endpoint:

Difference between 7-day average 24-hour pain (evaluated at patient level) on an 11 point NRS scale (0 = no pain and 10 = worst pain imaginable) measured during the final follow-up week of the treatment cycle (Week 16) among pathways. The NRS 24 hour average pain is now 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 (15,24,38).

4.3 Secondary Endpoints:

Efficacy

1. Difference between 7-day average 24-hour pain (evaluated at patient level) on an 11 point NRS scale at Week 6 among monotherapies.
2. Difference between RAND SF-36 physical mean scores (evaluated at patient level) at week 16 among pathways(39)
3. Difference between RAND SF-36 physical mean scores (evaluated at patient level) at week 6 among pathways (39)
4. Difference between RAND SF-36 mental mean scores (evaluated at patient level) at week 16 among pathways (39)
5. Difference between RAND SF-36 mental mean scores (evaluated at patient level) at week 6 among pathways (39)
6. Difference between Hospital Anxiety and Depression Scale (HADS) mean anxiety scores (evaluated at patient level) at week 6 among pathways. (40)
7. Difference between Hospital Anxiety and Depression Scale (HADS) mean anxiety scores (evaluated at patient level) at week 16 among pathways.(40)
8. Difference between Hospital Anxiety and Depression Scale (HADS) mean depression scores (evaluated at patient level) at week 6 among pathways. (40)
9. Difference between Hospital Anxiety and Depression Scale (HADS) mean depression scores (evaluated at patient level) at week 16 among pathways.(40)
10. Difference in proportion of patients having treatment success (30%) at week 16 among pathways. Treatment success is defined as a reduction in 30% value at follow up compared to baseline.
11. Difference in proportion of patients having treatment success (50%) at week 16 among pathways. Treatment success is defined as a reduction in 50% value at follow up compared to baseline.
12. Difference in BPI-MSF measure of pain interference with function total score (evaluated at patient level) at week 6 among pathways (41).
13. Difference in BPI-MSF measure of pain interference with function total score (evaluated at patient level) at week 16 among pathways (41).
14. Difference in Insomnia Severity Index (evaluated at patient level) total score at week 6 among pathways. (42)
15. Difference in Insomnia Severity Index (evaluated at patient level) total score at week 16 among pathways. (42)
16. Difference in Patient Global Impression of Change (evaluated at patient level) at week 16 among pathways (43).
17. Difference in proportion of care pathway preferred by participants at week 50.

Cost Effectiveness

18. EuroQoL-5D-5L: The EQ-5D is a routinely used generic health related quality of life (HRQL) instrument. It is the preferred instrument for assessing HRQL by NICE, and the newer five-level (EQ-5D-5L) instrument offers increased sensitivity as opposed to the original three-level version (44).
19. A modified version of the Client Service Receipt Inventory (CSRI): The CSRI is a routinely used instrument to capture health resource use and personal expenses. Unnecessary questions will be removed to reduce participant burden (45).

Safety

20. Frequency and proportion of patients reporting at least one Adverse Event for each of the pathway. Additionally the relationship to intervention (Definite, Probable,

Possible, Unlikely, Unrelated, Not assessable) will be reported (frequency and proportion).

21. Frequency and proportion of Adverse Events for each of the pathways.
22. Listing of Adverse Events for each of the pathways.
23. Frequency and proportion of patients reporting at least one Serious Adverse Event for each of the pathways. Additionally, these characteristics will be summarised (frequency and proportion): Intensity (Mild, Moderate, Severe), relationship (Definite, Probable, Possible, Unlikely, Unrelated, Not assessable), is SUSAR, is Death.
24. Frequencies of Serious Adverse Events for each of the pathways.
25. Listing of Serious Adverse Events for each of the pathways.

Subgroup

Neuropathic Pain Symptom Inventory (NPSI) questionnaire for subgroup analysis relating pain phenotype to treatment response (46). There is emerging evidence that treatment response may be determined by a patient's pain phenotype (47–49). In particular these outcomes will be evaluated:

26. Difference between "Burning (superficial) spontaneous pain" NPSI mean subscores - (evaluated at patient level) at week 6 among pathways.
27. Difference between "Burning (superficial) spontaneous pain" NPSI mean subscores - (evaluated at patient level) at week 16 among pathways.
28. Difference between "Pressing (deep) spontaneous pain" NPSI mean subscores - (evaluated at patient level) at week 6 among pathways.
29. Difference between "Pressing (deep) spontaneous pain" NPSI mean subscores - (evaluated at patient level) at week 16 among pathways.
30. Difference between "Paroxysmal pain" NPSI mean subscores - (evaluated at patient level) at week 6 among pathways.
31. Difference between "Paroxysmal pain" NPSI mean subscores - (evaluated at patient level) at week 16 among pathways.
32. Difference between "Evoked pain" NPSI mean subscores - (evaluated at patient level) at week 6 among pathways.
33. Difference between "Evoked pain" NPSI mean subscores - (evaluated at patient level) at week 16 among pathways.
34. Difference between "Paresthesia/dysesthesia" NPSI mean subscores - (evaluated at patient level) at week 6 among pathways.
35. Difference between "Paresthesia/dysesthesia" NPSI mean subscores - (evaluated at patient level) at week 16 among pathways.
36. Difference between NPSI mean total scores - (evaluated at patient level) at week 6 among pathways.
37. Difference between NPSI mean total scores - (evaluated at patient level) at week 16 among pathways.

Patient Perceived Tolerability

38. Difference between tolerability (evaluated at patient level) on an 11 point NRS scale at week 16 among pathways.
39. Difference between tolerability (evaluated at patient level) on an 11 point NRS scale at week 6 among monotherapies.

5. Ancillary sub-studies

5.1 Health Economic Evaluation

We will complete an economic evaluation as part of the study in order to understand the relative cost-effectiveness of the three treatment pathways.

A cost-utility analysis alongside the clinical study will be conducted. This will estimate the mean differences in costs, Quality Adjusted Life Years (QALYs), and report the incremental cost-effectiveness ratio (ICER) for each Treatment Pathway. The cost-utility analysis will be conducted in line with the NICE Guide to the Methods of Technology Appraisal (2013) (50). In particular, an NHS and Personal Social Services (PSS) perspective will be taken for costs, and health benefits will be quantified using QALYs.

The study will allow the mean four-month costs and QALYs for each Treatment Pathway to be estimated. QALYs will be estimated using the EQ-5D-5L questionnaire reported at baseline, week 6 and week 16 of each pathway. 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 (44).

NHS resource use will be measured for each participant between baseline and the final follow-up (before crossover/end of follow-up). This will include all medication costs, visits to health services, 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 using the widely used and validated Client Service Receipt Inventory (CSRI) questionnaire. Unnecessary questions in the CSRI will be removed to reduce the burden for participants; however questions relating to personal costs incurred and time-off-work (where relevant) will be retained for sensitivity analysis. Bootstrapped estimates of the ICERs will be sampled to allow the probability of each intervention of being cost-effective to be determined. This will be reported numerically, as well as visually by providing Cost Effectiveness Acceptability Curves (CEACs) (51).

A secondary sensitivity analysis will be undertaken with a wider societal perspective for costs. Personal costs and time off work will be included, as reported by participants using the CSRI questionnaire.

5.2 Blood Sample Storage

OPTION-DM will store blood samples for future research projects.

Blood samples will be stored for participants who have given additional consent for their blood to be stored for future research which may include genetic analysis. The samples will be obtained at the same time as other study blood samples. The blood may be shipped directly to a central lab or may be frozen and stored locally before being shipped to a central laboratory. Detailed information on the labelling, handling, storage and shipment of these specimens will be provided in the OPTION-DM Sample Collection Manual.

Samples from participants who stop study treatment or follow up early will be kept and used in future research unless the participant requests otherwise.

6. Selection and withdrawal of participants

6.1 Recruitment

Participants will be recruited from 8 secondary care DPNP centres (see Section 1.5). A number of approaches will be used to identify potential participants:

1. Hospital database searches will be completed at each of the participating sites.
2. Potential patients may be identified during routine hospital appointments at a study centre.
3. The GP patient registers at around 80 GP surgeries aligned to the participating centres will be checked for patients with a diagnosis of diabetes and prescriptions for neuropathic pain medications.
4. Participant Identification Centres (PIC) will be utilised.
5. Community podiatry services will be engaged to encourage referrals of potential patients, if applicable.
6. Details of the study will be advertised through the use of posters and leaflets in various clinics (for example diabetes outpatient clinics or GP surgeries).
7. The study will be advertised in a number of locations such as on charity websites, in local libraries, local newspapers and via local radio stations to inform potential participants about the study.

Participants identified through database searches or via the GP or PICs will be sent an invitation letter along with the participant information sheet. These will contain details of the local study team to contact for further information. Advertising materials will also contain contact details for further information.

All potential participants will be sent a copy of the participant information sheet to read prior to attending the screening visit to allow adequate time to consider the study.

Potential participants may also be contacted by telephone prior to attending the screening visit. During this call, site staff can answer questions and provide an overview of the study along with a summary of the key eligibility criteria. This will allow the potential participant the opportunity to assess whether the study is right for them before attending for the screening visit.

Additional Recruitment Processes in Scotland

The Scottish Diabetes Research Network (SDRN) holds a national register of patients with diabetes in Scotland who have expressed a willingness to be involved in research and have given consent to be approached regarding research studies. Alongside this database is another system of research register called The Scottish Health Research Register (SHARE) (https://www.registerforshare.org/). Some patients are now signed up to the SDRN register and the SHARE register simultaneously, others have signed up to either SDRN or SHARE registers separately. Due to the nature of the SDRN and SHARE registers, patients are not uniformly distributed across Scotland; consequently this is likely to be an efficient method of recruitment in some Health Boards but not in others.

Patients will be identified in the following ways –

a) When attending diabetes related clinics throughout Scotland. The research nurses will review routine diabetes, renal and retinal screening clinic lists in order to identify potential patients.

b) From lists of patients who have consented to be contacted about research studies, either through the SDRN Research Register or the Scottish Health Research Register (SHARE). The SDRN Research Register Manager, and the SHARE team, will carry out searches of their Research Registers to identify potential patients, following established processes. For the SDRN register, the SDRN core team will provide lists of potentially eligible participants to contacts in each health board via NHS email address or (in the case of SHARE-SDRN or SHARE register patients) a list of all suitable patients will be uploaded to a recruitment tracker hosted by the Health Informatics Centre (HIC), and accessible via secure login by each research nurse. Each nurse will only receive details of patients eligible within their area. Potentially eligible patients on the SDRN register will be contacted using their preferred method of contact – letter, phone call or email and subsequently mailed a participant information sheet.

c) Where patients with diabetes are managed in primary care then general practitioners may also be asked to identify and invite eligible patients to participate in the study. We may use the services of the Scottish Primary Care Research Network (SPCRN) and HIC to identify eligible patients, via SCI-Diabetes, and ask GPs to write to their patients.

d) The following methods of recruitment may also be used to invite patients to participate in the study –

□ Posters in local clinics and pharmacies

□ Advertisements on the DUK Scotland (Diabetes Research Trial Opportunities) website.

□ Advertisement on the MyDiabetesMyWay website.

□ Attendance at a diabetes education programme.

□ Patient information sheet. This will be sent to patients along with the GP patient invitation letter.

All posters/advertisements will request that patients contact the study project team to find out more about the study, and to ask about participation in the project. All documentation used will be approved by the research ethics committee (REC).

As the study progresses we will ask the study nurses to check the clinic lists against the study database for previous patient participation in order to avoid re-approaching patients who have either already participated, or declined to take part.

6.2 Inclusion Criteria

A participant is eligible for the study if the following criteria are met:

1. Participant aged ≥18 years
2. Neuropathic pain affecting both feet and / or hands for at least 3 months or taking pain medication for neuropathic pain for at least 3 months
3. Bilateral distal symmetrical neuropathic pain confirmed by the Douleur Neuropathique 4 (DN4) questionnaire at screening visit (52). The participant is eligible if 4 or more questions are answered as “yes”.
4. Bilateral distal symmetrical polyneuropathy confirmed by modified Toronto Clinical Neuropathy Score (mTCNS) > 5 at screening visit (53)
5. Stable glycaemic control (HbA1c < 108mmol/mol)
6. Participants will have a mean total pain intensity of at least 4 on an 11-point numeric rating scale (NRS; with 0 being ‘no pain’ and 10 ‘worst pain imaginable’) during 1 week off pain medications (Baseline Period). Patients could be invited to

attend Randomisation Visit sooner if it's clear that their mean pain score for the week is above 4 i.e. as soon as the total sum of the pain scores is ≥ 28 (e.g. randomisation could take place after 3 days if a patient scores 10 on each of the first 3 days of monitoring). This is to minimise the length of time patients remain off neuropathic pain treatments.

7. Willing and able to comply with all the study requirements and be available for the duration of the study. This will be a 1 year study in which all participants will undergo all Treatment Pathways regardless of treatment response and this point will be made clear
8. Willing to discontinue current neuropathic pain relieving medications
9. Informed consent form for study participation signed by participant

6.3 Exclusion Criteria

A participant is not eligible for the study if any of the following criteria are met:

1. Non-diabetic symmetrical polyneuropathies
2. History of alcohol/substance abuse which would, in the opinion of the investigator, impair their ability to take part in the study
3. History of severe psychiatric illnesses which would, in the opinion of the investigator, impair their ability to take part in the study
4. History of epilepsy
5. Contraindications to study medications
6. Pregnancy/breast feeding or planning pregnancy during the course of the study
7. Use of prohibited concomitant treatment (as detailed in section 8.10) that could not be discontinued with the exception of prior concomitant and safe use of selective serotonin reuptake inhibitors (SSRIs) with study medication (duloxetine and/or amitriptyline). Note that concomitant use of citalopram is not permitted
8. Use of high dose morphine equivalent (>100mg/day)
9. Liver disease (AST/ALT >2 times upper limit of normal)
10. Significant renal impairment (eGFR <30mL/minute/1.73m^2)
11. Heart failure New York Heart Association (NYHA) ≥ class III
12. Clinically significant cardiac arrhythmias on 12 lead ECG,current history of arrhythmia, second or third degree heart block or left bundle branch block (patients with right bundle branch block or first degree heart block may be included following discussion with cardiology team)
13. Patients with a recent myocardial infarction (<6 months prior to randomisation)
14. Symptomatic postural hypotension which in the opinion of the investigator is clinically significant and would be a contraindication to the study medication
15. Prostatic hypertrophy or urinary retention to an extent which would, in the opinion of the investigator, be a contraindication to the study medication
16. Patients with other painful medical conditions where the intensity of the pain is significantly more severe than their diabetic peripheral neuropathic pain (patients will not be excluded if the pain is transient in nature)
17. Any suicide risk as judged by the investigator or as defined by a score of ≥2 on the suicide risk questionnaire
18. Significant language barriers which are likely to affect the participants understanding of the medication schedule or ability to complete outcome questionnaires
19. Concurrent participation in another clinical trial of an investigational medicinal product

20. Major amputations of the lower limbs
21. Foot ulcers, only if in the opinion of the local PI will have a confounding/detrimental effect on study primary outcome or participation e.g. localised foot pain from the ulcer site

6.4 Informed Consent Process

Prior to randomisation, written informed consent to enter the study must be obtained from participants. This will be done once they have had adequate time to consider the Participant Information Sheet, after explanation of the aims, methods, potential benefits and hazards of the study and before any study specific procedures are performed. This will be carried out by a medically qualified site Investigator.

Throughout the consent process it must be made completely and unambiguously clear that participation in the study is entirely voluntary and that consent regarding study participation may be withdrawn at any time without affecting their future care.

The participant will receive a copy of the consent form and the original will be filed in the Investigator Site File. A second copy will be kept with the participant's notes. The consent process will also be documented in the participant notes with a signed and dated note to confirm that informed consent was obtained for the study.

A letter will be sent to the participant's general practitioner (GP) informing him/her of the study and the participant's involvement in it once they have been randomised.

6.5 Screening Procedures and Pre-randomisation Investigations

After providing consent, participants will be instructed on how to washout neuropathic pain medication (Section 6.5.2) before commencing a one-week period of baseline pain monitoring. It is acceptable to delay the washout and baseline periods by 2-3 weeks if necessary provided the randomisation visit is scheduled no more than 4 weeks after the initial screening visit.

Participants will be assigned the next sequential study ID from a site specific screening log. This study ID will be used throughout the study.

6.5.1 Screening Visit (Week -2)

During the Screening Visit the following will be completed:

- Medical history (including detailed neuropathic pain history and previous medications)
- Ethnicity
- Suicidal risk questionnaire (self-completed or administered by the study team)
- Vital signs (height, weight, heart rate and blood pressure [lying and standing])
- Review of concomitant medications
- A full physical and neurological assessment to ensure the presence of a distal symmetrical polyneuropathy that starts in the feet
- mTCNS and DN4 will be used to screen for the presence of DPNP
- Assessment of brush-evoked allodynia
- Full blood count
- Urea and electrolytes
- Liver function tests including AST and ALT
- Glycosylated haemoglobin A1c

- Serum creatinine
- 12 lead ECG
- All patients with foot ulcers should have a documented ankle brachial pressure index (ABPI) for the affected foot unless the pulse is palpable. Previous results can be used if ABPI performed within previous 6 months. Note that if a foot ulcer occurs during protocol treatment, ABPI will be recorded for the affected foot unless the pulse is palpable.

During this visit, participants will be assessed for any suicidal ideation. If there is any concern that the participant is at risk the study team will notify the GP of these concerns. Where possible, this will be discussed with the participant first. If there is a real concern that the participant may be at immediate risk, more urgent action will be required. This may involve a referral to the community mental health team or the implementation of local risk management policies.

6.5.2 Initial Washout Period

Participants will be instructed to taper off neuropathic pain medications over one week (Initial Washout Period). The dose will be tapered for 3 days with complete washout for 1-4 days at the investigators discretion. If the participant is on combination therapy then all drugs will be tapered at once. Participants who are not taking any neuropathic pain medications at the screening visit can enter straight into the baseline period i.e. the initial washout period is not relevant for these participants.

For participants taking 50-100mg morphine equivalent the dose will be tapered over a period of up to 2 weeks. Participants then enter the baseline period i.e. no additional washout period is necessary. It is recommended that the dose is halved every three days however investigator discretion should be used in patients at increased risk, for example older patients or those with a history of heart disease. Similarly for participants taking duloxetine the dose can be tapered over 3 days or over a period of up to 2 weeks depending on symptoms encountered on a case-by-case basis.

Participants will also be provided with daily pain diaries along with instructions of how to complete these. Each morning participants will be asked to record:

- Total pain experienced over the preceding 24-hours, rated once daily, using an 11-point NRS.
- The amount of rescue medication used.

Pain scores may also be collected via daily text messages where participants have given additional consent for this.

Telephone contact will be maintained by the research nurse over the initial washout period to review progress. Up to a total of 1g paracetamol QDS will be allowed as rescue medication during all study phases.

6.5.3 Baseline Period

Following the Initial Washout Period, participants will enter the Baseline Period.

From the daily pain scores collected during the baseline period, a mean for the week will be determined and used in subsequent analysis. Patients could be invited to attend Randomisation Visit sooner if it's clear that their mean pain score for the week is above 4 i.e. as soon as the total sum of the pain scores is ≥28 (e.g. randomisation could take place after 3

days if a patient scores 10 on each of the first 3 days of monitoring). This is to minimise the length of time patients remain off neuropathic pain treatments.

6.5.4 Randomisation Visit (Week 0)

Baseline Period pain diaries will be collected and study eligibility will be verified. The following will also be performed:

- Review of concomitant medications
- Pregnancy test (only for women of child bearing potential). Note that the result of this test must be checked prior to randomisation to ensure the participant is eligible for the study.
- Neuropathic pain assessment:
    - Pain diaries will be checked to confirm participants ' eligibility (mean NRS pain score ≥4)
    - The quality of neuropathic pain will be assessed by completion of the Neuropathic Pain Symptom Inventory (NPSI)
    - Pain interference with function using the Brief Pain Inventory-Modified Short Form (BPI -MSF)
- Psychological and quality of life assessments:
    - Insomnia Severity Index (ISI)
    - Hospital Anxiety and Depression Scale (HADS)
    - RAND SF-36
    - EuroQol -5D-5L
    - Modified health resource questionnaire based on Client Service Receipt Inventory (CSRI) to capture health resources used.
    - Tolerability scale
    - Pain catastrophizing scale

Upon completion, participants will be randomised to one of six treatment sequences. Once a participant has been randomised, the site pharmacist will access the database to find out the treatment allocation. Only the pharmacist will be given access to this information in the database.

Study medications will be dispensed by the pharmacist and participants instructed to take the first dose. Note that the first dose can be started on the same day as randomisation or the following morning at the discretion of the investigator however care should be taken to ensure that the week 1 assessments occur within 7 days (+/- 2) of starting treatment. New diaries will be provided and participants reminded to complete 24-hour average pain scores daily throughout the study. Pain scores may also be collected via daily text messages where participants have given additional consent for this.

Telephone contact (at least once a week) will be maintained by the research nurse to ensure compliance to treatment and completion of diaries.

6.6 Co-enrolment Guidelines

Concurrent participation in any other clinical study of an investigational medicinal product is not allowed for the duration of the study. Participation in other studies may be acceptable in accordance with local guidelines and with agreement from the Chief Investigator or delegate.

6.7 Early Stopping of Protocol Treatment

An individual participant may stop treatment early for any of the following reasons:

- Unacceptable toxicity
- Withdrawal of consent for treatment by participant
- Inter-current illness which prevents further treatment
- Any alteration in the participant's condition which justifies the discontinuation of treatment in the investigator's opinion
- Pregnancy

As participation is entirely voluntary, the participant may choose to discontinue study treatment at any time. Although the participant is not required to give a reason for discontinuing their study treatment, a reasonable effort will be made to establish this reason while fully respecting the participant's rights.

If study treatment is discontinued, for whatever reason, this will be documented on the relevant CRF and the participant will continue to be followed up until Week 16 of the current treatment pathway, providing they are willing. If not, they will be asked to attend for a visit as soon as possible to complete final assessments (as per the week 16 assessments in the Study Assessment Schedule). A discussion will also take place to clarify whether the participant wishes to stop all protocol treatment or whether they wish to come back for the next treatment pathway.

6.8 Early Stopping of Follow-up

Participants stopping follow-up early have a negative impact on a study's data. Centres will explain the importance of remaining on study follow-up however if participants do not wish to remain on study follow-up their decision must be respected.

If the participant explicitly states their wish not to contribute further data to the study, the CTRU will be informed in writing. However, data up to the time of consent withdrawal will be included in the data reported for the study.

Participants who stop study follow-up early will not be replaced.

7. Randomisation

At Visit 2 (Randomisation Visit), after confirming the eligibility of the participant and performing all baseline assessments (see section 6.4.4), the participant will be centrally randomised in the study using the CTRU online randomisation system (SCRAM). Participants will be assigned to one of the six sequences (allocation 1:1:1:1:1:1) based on a predetermined randomisation schedule stratified by study site using permuted blocks. The block sizes will not be disclosed, to ensure concealment. The study blind will not be broken except in an emergency or regulatory requirement.

8. Treatment of Participants

Participants will be randomised to one of six sequences. Each sequence consists of 3 Treatment Pathways:

- A-P Pathway (First line amitriptyline, second line pregabalin)

- D-P Pathway (First line duloxetine, second line pregabalin)
- P-A Pathway (First line pregabalin, second line amitriptyline)

Treatment is blinded and placebo-controlled therefore the dosing schedule is identical across the three pathways.

8.1 IMP Details

Study treatment will be supplied to sites in bottles containing tear-off labels which will identify the medication. The study pharmacist will remove the tear-off label prior to dispensing. Blinding will be maintained with over-encapsulated drugs and matching placebos.

Study treatment will be supplied in capsules of the following doses:

- Amitriptyline – 25mg capsules
- Amitriptyline – 50mg capsules
- Duloxetine – 30mg capsules
- Pregabalin – 75mg capsules
- Pregabalin – 150mg capsules
- Matching placebo capsules

Capsules will be supplied in bottles containing either 9 capsules, 23 capsules or 51 capsules.

Participants will be instructed to take study medication orally before breakfast and at bedtime. The total daily dose of each drug will vary depending on the dose level. Please refer to Table 1 below for details of the dosing schedule. Participants will be carefully instructed on the dosing of study medication during each treatment period. This will be reinforced with written instructions and a medication diary provided at each dispensing visit.

A prescription is required at each dispensing visit and this must be signed by an investigator who has been delegated this task by the PI. The prescription must only be signed after all study assessments have been completed. Where necessary, assessments can be completed by telephone to allow the prescription to be completed in advance of the visit. Please refer to the OPTION-DM research manual for further details.

If a participant forgets to take a tablet they will be advised to take it within 5 hours of the time that they usually take it. They will be advised to delay the next dose slightly, if possible.

Table 1: Dosing schedule by dose level

		Amitriptyline	**Duloxetine**	**Pregabalin (standard*)**	**Pregabalin (reduced**)**
Dose Level 1	AM	1 x placebo	1 x placebo	1 x 75mg	1 x 75mg
	PM	1 x 25mg	1 x 30mg	1 x 75mg	Placebo
Dose Level 2	AM	1 x placebo	1 x 30mg	1 x 150mg	1 x 75mg
	PM	1 x 50mg	1 x 30mg	1 x 150mg	1 x 75mg
Dose Level 3	AM	2 x placebo	2 x 30mg	2 x 150mg	2 x 75mg
	PM	1 x 25mg & 1 x 50mg	2 x 30mg	2 x 150mg	2 x 75mg

*Standard pregabalin doses to be used where latest eGFR result is ≥60ml/min

**Reduced pregabalin doses to be used where latest eGFR result is 30-59ml/min

8.2 Dose Titration

Participants will be titrated to a maximum tolerated dose level on starting each of the treatment pathways and at initiation of second line treatment, if applicable. The schedule of dose escalation will be identical in each Treatment Pathway. There are two dosing schedules for pregabalin based on the latest eGFR result. eGFR will be measured at screening and at week 16 of each pathway. Pharmacy must be informed of the latest eGFR result with each prescription in order to ensure that the correct dose of pregabalin is dispensed. At each dispensing visit, prior to completing the prescription, blood results must be checked in case an updated eGFR result is available. If eGFR changes during a pathway, the pregabalin dosing will be amended accordingly.

When a new treatment is started, the dose will be escalated one dose level at a time towards the maximum tolerated dose or maximum permitted dose, whichever is first, (see Figure 2). Decisions will be based on treatment response (based on the 24-hour pain NRS score), side effect profile and participant preference. Dose titration decisions will usually be made during the first 2 weeks of each treatment phase however changes can be made to the dose at any time if deemed necessary by the investigator. This may lead to deviations from the planned titration schedule in order to make the trial as pragmatic as possible.

At weekly intervals, the research nurse will evaluate response to treatment and adverse effects to guide dose titration accordingly. If patients are receiving adequate pain relief (24-hour pain NRS score ≤3) at dose level 1 or 2 then the dose will not be increased further.

Patients will be asked to report any side effects and these will be graded as mild, moderate or severe by the nurse or investigator. The patient will be asked to rate whether side effects are tolerable or intolerable. Any severe or intolerable side effects will require a medication review (i.e. consider dose reduction or discontinuation). The patients overall condition should also be taken into account when making dose titration decisions, including age and other comorbidities. In case of significant intolerability, based on investigator and participant decision, the dose will be reduced by one dose level. Detailed guidance on dose titration will be provided in a study-specific SOP.

Participant preference will be taken into account where possible when making dose titration decisions. However, the dose must not be escalated based on participant preference alone i.e the decision to increase the dose must be based on treatment response and side effect profile.

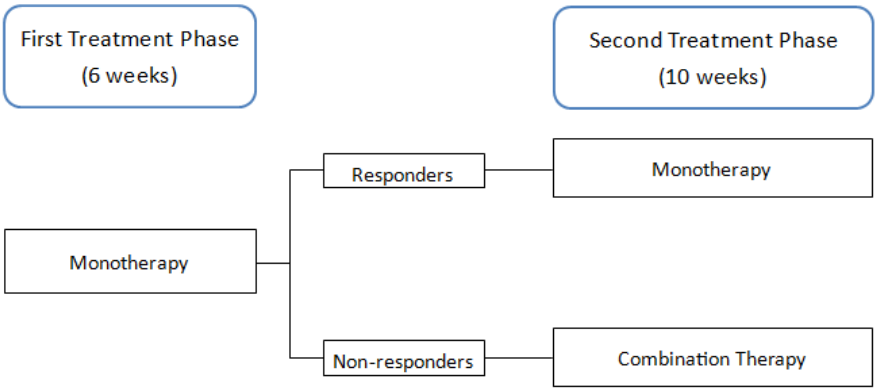
In the third week of each treatment phase, each participant will usually receive his or her maximal tolerated dose for the particular treatment. At the end of each treatment pathway, participants will undergo three days of dose tapering and four days of complete washout.

Dose level will not be blinded (to the research team or participants). The local pharmacy will add details of the dose level, i.e. Dose Level 1, 2 or 3, to the medication bottles prior to dispensing.

8.3 Treatment Phases

Each Treatment Pathway is split into two treatment phases.

Figure 4: Two treatment phases per pathway



8.3.1 First Treatment Phase

During the first treatment phase, participants will receive monotherapy with the first line treatment in the pathway. This will last for a total of 6 weeks, including the dose titration phase.

Table 2: Dispensing Schedule (first treatment phase)

	Week No.	Dose Level Dispensed	Amount of drug supplied	Guidance
Dose Titration	Week 0*	Dose Level 1	2 week supply	Dispense dose level 1 for 2 weeks. Participant to take dose level 1 during the first week.
		Dose Level 2	1 week supply	Dispense dose level 2 for 1 week. Participant not to take dose level 2 unless instructed by the study nurse at week 1 telephone call.
	Week 1	NA – telephone call	NA – telephone call	Dose review with study nurse. Participant instructed to continue on dose level 1 or to increase to dose level 2 based on adverse events and efficacy.
Dose Maintenance	Week 2	Maximum Tolerated Dose	1 week supply	Dose review with study nurse. Dispense agreed dose level for 1 week.
	Week 3	Maximum Tolerated Dose	3 week supply	Dose review with study nurse. Dispense agreed dose level for 3 weeks.

*It is expected that the dose titration decisions at week 1 will take place via a telephone call with the study nurse (as per Table 2) however it is acceptable to schedule a visit at week 1 (instead of the telephone call) if required. In this case, only a 1 week supply of study medication will be dispensed to the participant at week 0. The week 1 medication will be given to the participant when they attend for the week 1 visit and only the required dose level will be provided.

At the week 6 follow-up visit a decision will be taken to either continue on monotherapy or to commence combination therapy with the addition of the second line treatment in the pathway. This decision will be based on the 7-day average 24-hour pain NRS score during the

week preceding the study visit. Participants will be divided into 'responders' (pain score ≤3) and 'non-responders' (pain score >3) and this will be used to guide treatment during the second treatment phase (54). Note that if a patient is on dose level 1 or 2 of first line treatment it is acceptable to increase the dose of first line treatment at week 6 rather than start second line treatment. This decision is at the discretion of the local investigator. In this case, the patient should be reviewed closely over the next few weeks to assess whether initiation of second line treatment is indicated at a later visit.

For participants whose pain score has not reduced at all since baseline, or if it has increased, please refer to section 8.3.3 for details on switching to second line treatment as a monotherapy.

In the event that a participant is a 'responder' at week 6 but becomes a 'non-responder' later in the second treatment phase, second line treatment can be started up to week 13. The dose titration will follow the same schedule.

8.3.2 Second Treatment Phase

The second treatment phase will last for a total of 10 weeks. Responders will continue on monotherapy for the remainder of treatment phase 2. Non-responders will commence combination therapy with the addition of second line treatment for 10 weeks, including the dose titration phase.

The dispensing schedules are detailed in the tables below. For responders only table 3 will be relevant but for non-responders, dispensing will take place according to both table 3 and table 4.

Table 3: Dispensing Schedule (monotherapy during second treatment phase)

	Week No.	**Dose Level Dispensed**	**Amount of drug supplied**	**Guidance**
Dose Maintenance	Week 6	Maximum Tolerated Dose	3 week supply	Review with study nurse. Dispense agreed dose level for 3 week.
	Week 9	Maximum Tolerated Dose	7 week supply	Review with study nurse. Dispense agreed dose level for 7 week.

Table 4: Dispensing Schedule (combination therapy during second treatment phase)

	Week No.	Dose Level Dispensed	Amount of drug supplied	Guidance
Dose Titration	Week 6*	Dose Level 1	2 week supply	Dispense dose level 1 for 2 weeks. Participant to take dose level 1 during the first week.
		Dose Level 2	1 week supply	Dispense dose level 2 for 1 week. Participant not to take dose level 2 unless instructed by the study nurse at week 1 telephone call.
	Week 7	NA – telephone call	NA – telephone call	Dose review with study nurse. Participant instructed to continue on dose level 1 or to increase to dose level 2 based on adverse events and efficacy.
Dose Maintenance	Week 8	Maximum Tolerated Dose	1 week supply	Dose review with study nurse. Dispense agreed dose level for 1 week.
	Week 9	Maximum Tolerated Dose	7 week supply	Dose review with study nurse. Dispense agreed dose level for 7 weeks.

* It is expected that the dose titration decisions at week 7 will take place via a telephone call with the study nurse (as per Table 4) however it is acceptable to schedule a visit at week 7 (instead of the telephone call) if required. In this case, only a 1 week supply of second line treatment will be dispensed to the participant at week 6. The week 7 medications will be given to the participant when they attend for the week 7 visit and only the required dose level will be provided.

8.3.3 Switching Treatment during a Pathway

At the week 6 visit, if the average pain score over the last week does not show any improvement since the start of the pathway, participants will switch to the second line treatment in the Treatment Pathway i.e. the second line treatment will be started as a monotherapy and will be continued until the end of the pathway. Second line treatment can be started immediately without the need to washout first line treatment.

If there is significant intolerance to first line treatment, participants can switch to the second line treatment in the Treatment Pathway. In this situation the switch can be made immediately, at any time, without the need to washout the first line treatment. The second line treatment will be continued for the remainder of the treatment pathway i.e. up to the week 16 visit.

If there is significant intolerance to the second line treatment in the pathway, the participant will stop study treatment but will remain in the study for follow up.

8.3.4 Taper Doses

At the week 16 follow-up visit, participants will be advised to taper down study medication (3 days) and stop the medication completely (4 days) before commencing the next treatment pathway. The taper dose will be one dose level below the maximum tolerated dose as per the table below:

Table 5: Taper Dose Levels

Maximum Tolerated Dose Level	Taper Dose Level
1	No taper dose required
2	1
3	2

Where there are significant withdrawal side effects then the medication can be tapered down more gradually according to the judgement of the investigator. However, the patient must still completely stop the medication for at least 4 days before starting the next pathway.

The first and second treatment phases will be repeated until the participant completes all three pathways.

8.4 Dispensing

Participating centres will be provided with a start-up supply of study medication once the centre has been opened to recruitment by CTRU. The IMP will be stored separately from routine clinic drug supplies in a designated section of the pharmacy and in a dry, safe place according to the Summary of Product Characteristics (SmPC). A study-specific pharmacy manual will be provided containing detailed instructions for the centre pharmacist.

Bottles of IMP will be supplied with a tear off label to maintain the blinding. Prior to dispensing the treatment, the centre pharmacist will remove the tear off label and add a local label. Detailed instructions will be provided in the OPTION-DM Pharmacy Manual.

Participants will be requested to return all empty bottles and unused medication when they attend for follow up visits.

At each centre, the pharmacist will be required to maintain complete records of all study medication dispensed and returned and this will be documented on the OPTION DM Accountability Logs.

8.5 Accountability

Procedures for drug distribution, accountability and destruction will be detailed in the OPTION-DM Pharmacy Manual. Drug accountability will be regularly monitored and the remaining stocks checked against the amounts dispensed.

8.6 Adherence

Participants will be provided with detailed guidance regarding how to take their study medication. This will be reinforced with written instructions and participants will be directed to complete a daily medication diary to record which doses they have taken.

Participants will be asked to return all bottles of study medication, including empty bottles and any unused medication. These will be reviewed and remaining capsules counted to monitor adherence to study treatment. The study nurse will provide further guidance to participants if there is concern about adherence levels.

8.7 Dose Modifications and Interruptions

Modifications/interruptions to study medications will be allowed as needed.

Changes in a participant's eGFR may require a change to the dosing of pregabalin. eGFR is assessed as standard at week 16 of each pathway and this will determine the pregabalin dosing schedule for the next pathway. If the investigator becomes aware that a participant's eGFR has increased to ≥60ml/min or decreased to 30-59ml/min during a pathway, the site staff must contact CTRU for advice.

Any modifications/interruptions to study medications whilst patients are on maximum tolerated doses will be recorded on the CRF. Patients will be allowed to remain in the study at the discretion of the local PI however any interruption to treatment of longer than one week will be discussed with the CTRU.

8.8 Overdose of Study Treatment

Participants will be counselled on the importance of taking the study medications as prescribed. In the event that an overdose of study medication does occur, the participant will contact the local OPTION-DM study team as soon as possible to receive appropriate advice. Participants will be provided with an out of hours contact number but will be advised to attend A&E in the case of an emergency. Participants will then be managed on a case by case basis and toxicity will be managed according to standard practice.

If necessary, emergency unblinding is available (please see section 8.9 below).

8.9 Unblinding

Randomisation codes will be held by CTRU. All participants will be unblinded at the end of the study, when the final statistical report has been completed. Participants will be provided with their pain scores and Global Impression of Change Scores along with their allocated treatment sequence (further details in the Statistical Analysis Plan, SAP).

Since blinding is critical to the integrity of the study, unblinding a participant's study treatment during the study is strongly discouraged unless it is a medical emergency and will alter clinical management.

8.9.1 Emergency Unblinding

Unblinding will generally only be considered in the event of a medical emergency where knowledge of the participant's treatment allocation would change the clinical management.

Where unblinding is being considered during work hours (Mon – Fri, 09:00 – 17:00 UK time), the case will normally be discussed with CTRU first however the investigator may unblind the treatment allocation immediately if deemed necessary. Out of hours, the investigator (or assigned deputy) will have determined that the information is necessary i.e. that it will alter the participant's immediate management. Where it is deemed necessary, a member of site staff will be responsible for unblinding the treatment allocation out of hours. This will be performed according to the OPTION-DM Unblinding SOP.

Unblinding for any purpose other than a medical emergency is generally not permitted but individual cases will be discussed with CTRU if it is believed to be necessary for the medical care of the participant.

For any treatment code unblinding, the reason for the decision to unblind and the parties involved will be documented on the unblinding CRF. Treatment identification information will be kept confidential and will be disseminated only to those individuals that must be

informed for medical management of the participant. Wherever possible, the study teams involved in the day-to-day running of the study will remain blinded.

8.9.2 Unblinding for Safety Reporting

A member of staff at CTRU will unblind the treatment allocation and will be responsible for reporting any Suspected Unexpected Serious Adverse Reactions (SUSARs) as appropriate. Treatment identification information will be kept confidential and will be disseminated only to those individuals that must be informed.

8.10 Concomitant Medications

Participants will maintain their current schedule of treatment throughout the duration of the study. Changes to concomitant medications will be documented at each study visit. The following concomitant medications and treatments for pain are allowed during the study period:

- Paracetamol 1g up to a maximum dose of QDS.

The following concomitant medications are prohibited during the study period:

- Opioid analgesia
- Capsaicin cream/high dose capsaicin patches
- Lidocaine patches
- Anti-inflammatory medications (e.g. diclofenac, colecoxib)
- Other antiepileptic medications (e.g. carbamazepine)
- Other antidepressant medications (e.g. SSRIs, MAOIs) with the exception of prior concomitant and safe use of SSRIs and study medications (duloxetine and/or amitriptyline) i.e. prior to study entry (see Section 6.3). The combination of SSRIs and serotonin and norepinephrine reuptake inhibitors (SNRIs) is contraindicated unless there has been prior safe concomitant use due to the risk of serotonin syndrome. Even where there has been prior safe concomitant use, such participants should be warned to look out for symptoms of serotonin syndrome and report these immediately.
- Other neuropathic pain medications (e.g. venlafaxine, IV lignocaine etc.)
- Opsite patches
- Use of any medications that could lead to potentially serious interactions with study medications

Short term use of a prohibited medication may be allowable. All instances must be discussed with CTRU and recorded on the concomitant treatment CRF.

8.11 Pregnancy

As per the eligibility criteria, participants joining OPTION-DM will not be pregnant or breast feeding at randomisation. Participants will also be advised against becoming pregnant during the study treatment period and women of child bearing potential must have a highly effective contraception as detailed below:

- combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation
    - oral
    - intravaginal
    - transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation

    - oral
    - intravaginal
    - transdermal
- intrauterine device (IUD)
- intrauterine hormone-releasing system (IUS)
- bilateral tubal occlusion
- vasectomised partner
- true abstinence: when this is in line with the preferred and usual lifestyle of the participant.

If a participant becomes pregnant during the study, the study treatment will be discontinued and a pregnancy reporting form completed. The participant will remain in the study for follow up until the end of the pregnancy, provided they are willing. Informed consent will be obtained for this using the Pregnancy Information Sheet and Consent Form.

9. Assessments and procedures

9.1 Study Assessment Schedule

The study assessment schedule below details the assessments required during the course of one treatment pathway. All participants will complete 3 treatment pathways and this schedule will be repeated from week 0 to week 16 until all 3 pathways are complete. Week 17 will only be relevant at the end of the final pathway.

Assessments		Weeks from starting treatment pathway[b]							
	-2[a]	0[c]	2[c]	3[c]	6[c]	8[c,d]	9[c]	16[c, e]	17[f]
Informed consent	X								
Blood Tests[gh]	X							X	
ECG	X								
Medical History	X								
Physical and neurological assessment	X								
modified Toronto Clinical Neuropathy Score (TCNS)	X								
Douleur Neuropathique 4 (DN4)	X								
Suicidal risk questionnaire	X								
Concomitant Medications	X	X	X	X	X	X	X	X	X
Vital Signs[i]	X							X[m]	
Pregnancy Test (for women of child bearing potential)		X[k]		X	X		X	X	
Dispense Study Medication		X	X	X	X	X	X	X	
Pain Diaries[j]	X	X	X	X	X	X	X	X	
Tolerability scale		X[k]			X			X	
Brief Pain Inventory-Modified Short Form (BPI-MSF)		X[k]			X			X	
Insomnia Severity Index (ISI)		X[k]			X			X	
Neuropathy Pain Symptom Inventory (NPSI)		X[k]			X			X	
Hospital Anxiety and Depression Scale (HADS)		X[k]			X			X	
RAND Short Form 36 (RAND SF-36)		X[k]			X			X	
EQ-5D-5L		X[k]			X			X	
Client Service Receipt Inventory (CSRI)		X[k]			X			X	
Pain Catastrophising Scale (PCS)		X[k]							
Adverse Events Assessment		X[l]	X	X	X	X	X	X	X
Compliance Assessment		X[l]	X	X	X	X	X	X	X
Patient Global Impression of Change (PGIC)								X	

a. This visit is only required prior to randomisation i.e. before starting the first treatment pathway.
b. Between scheduled study visits, the research nurse will contact the participant by phone each week (a minimum of once per week). The nurse will confirm compliance with medication and remind the participant to complete study diaries/questionnaires.
c. Visits must normally be within +/- 2 days of the scheduled visit date. Where this is impossible, e.g. due to Bank Holidays or patient availability, contact CTRU for advice.
d. Week 8 visit only required for participants on combination treatment.
e. At the week 16 visit, participants will be given instructions to taper off the current study treatment (see section 8.3.3 for details). Visits from week 0 to week 16 will be repeated until all 3 pathways have been completed.
f. Week 17 is only applicable following the final pathway.
g. FBC, urea and electrolytes, liver function tests (including AST and ALT), glycosylated haemoglobin A1c and serum creatinine.
h. Whole blood sample to be collected and stored for future research. The sample can be obtained at the same time as any scheduled blood test for the study. Please refer to the OPTION-DM Sample Collection Manual for details.
i. Height (at week -2 only), weight, heart rate and blood pressure (lying and standing).
j. To be completed by participants daily during the study, starting during the washout period. Pain scores may also be collected via daily text messages where participants have given additional consent for this.
k. Only required at week 0 of pathway 1 i.e. randomisation visit.
l. Not required at week 0 of pathway 1 i.e. randomisation visit.
m. If the blood pressure reading at week 16 shows postural hypotension (>20mmHg), the BP will be repeated at week 0 of the next pathway to assess the participants suitability for continuing in the study.

9.2 Unscheduled Study Visits

Participants will be seen and assessments performed as detailed in the Study Assessments Schedule however, an unscheduled study visit will be organised if a patient is unable to tolerate the maximum dose of the study medication during the maintenance treatment phase. New study medication will be dispensed and the medication down-titrated to a previously tolerated dose. Any changes to study medication will be documented in the CRF.

9.3 Procedures for Assessing Efficacy

The NRS 24 hour average pain is considered the gold standard for the assessment of neuropathic pain. This will be assessed via pain diaries which will be given to participants at each study visit along with detailed instructions on how to complete them. Participants will be instructed to complete the diaries each morning during the study. Completed diaries will be collected at the subsequent visit.

9.4 Procedures for Assessing Safety

Safety assessments will be performed as detailed in the Study Assessment Schedule in Section 9.1.

- Blood tests will be performed at week 16 of each pathway
- Vital signs will be assessed at week 16 of each pathway
- Adverse events will be assessed during each study visit or telephone call.
- Concomitant medications will be reviewed during each study visit or telephone call.

9.5 Procedures for Assessing Neuropathic Pain

The following questionnaires will be completed as per the Study Assessment Schedule in Section 9.1 to assess neuropathic pain:

- Pain diaries
- Neuropathy Pain Symptoms Inventory (NPSI)
- Brief Pain Inventory-Modified Short Form (BPI-MSF)

Questionnaires can be completed during the visit. Alternatively, questionnaires can be posted to the participants in advance of the visit and the participants will be requested to bring the completed questionnaires when they attend their study visit. In the event that the participant forgets to bring the questionnaires or has not completed them, they will be provided with another copy to complete during the visit. Please note that these must be self-completed.

9.6 Procedures for Assessing Quality of Life, Psychological Wellbeing & Health Economics

The following questionnaires will be completed as per the Study Assessment Schedule to assess quality of life:

- Insomnia Severity Index (ISI)
- Hospital Anxiety and Depression Scale (HADS)
- RAND Short Form 36 (RAND SF-36)
- EQ-5D-5L
- Modified Client Service Receipt Inventory (CSRI)
- Patient Global Impression of Change (PGIC)
- Tolerability scale

Questionnaires can be completed during the visit. Alternatively, questionnaires can be posted to the participants in advance of the visit and the participants requested to bring the completed questionnaires when they attend their study visit. In the event that the participant forgets to bring the questionnaires or has not completed them, they will be provided with another copy to complete during the visit. Please note that these must be self-completed.

9.7 Loss to Follow-up

Participants will be considered lost to follow up if they fail to attend for a visit and all reasonable efforts to contact the participant by phone, text, letter and/or email, including contact on different days/at different times, have been unsuccessful.

9.8 Site and study closure procedures

The end of trial will be defined as the completion of all sample analyses associated with the trial (provided this occurs after the completion of last patient last visit). The regulatory authority and ethics committee will be notified within 90 days of the end of the trial. Participating sites will be closed once data cleaning is completed, even if this is prior to the end of the trial.

10. Safety Reporting

ICH GCP requires that both investigators and sponsors follow specific procedures when reporting adverse events/reactions in clinical studies. These procedures are described in this section of the protocol.

10.1 Definitions

The definitions of the EU Directive 2001/20/EC Article 2 based on the Principles of ICH GCP apply to this protocol. These definitions are given in Table 6 below.

Table 6: Definitions of Adverse Events and Reactions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a patient or clinical study patient to whom a medicinal product has been administered including occurrences that are not necessarily caused by or related to that product.
Adverse Reaction (AR)	Any untoward and unintended response to an investigational medicinal product related to any dose administered.
Unexpected Adverse Reaction (UAR)	An adverse reaction, the nature or severity of which is not consistent with the information about the medicinal product in question set out in the Summary of Product Characteristics (SmPC).
Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR) or Suspected Unexpected Serious Adverse Reaction (SUSAR)	Respectively any adverse event, adverse reaction or unexpected adverse reaction that: • Results in death • Is life-threatening* • Requires hospitalisation or prolongation of existing hospitalisation** • Results in persistent or significant disability or incapacity • Congenital anomaly/birth defect

	• Is another important medical condition***

**The term life-threatening in the definition of a serious event refers to an event in which the patient is at risk of death at the time of the event; it does not refer to an event that hypothetically might cause death if it were more severe, for example, a silent myocardial infarction.*

***Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition, that has not worsened or for an elective procedure do not constitute an SAE.*

****Other important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered a serious adverse event/experience when, based upon appropriate medical judgement, they may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.*

10.2 Study Specific Exemptions

The following events, in the context of this study, will not be considered SAEs. No SAE form is required and they are exempt from expedited reporting. They will however be recorded as an AE on the appropriate CRF:

- Elective hospitalisation for a pre-existing disease or a condition present before treatment that does not worsen

The following events, in the context of this study, will be considered as SAEs (if they meet the definition of serious in Table 6) but will be exempt from expedited reporting. An SAE form will be completed for these events and faxed to CTRU within 4 weeks of the event being discovered:

- Episodes of severe hypoglycaemia and diabetic ketoacidosis

10.3 Pregnancy

Women of childbearing potential are required to receive a highly effective form of contraception (See section 8.11 for details). Pregnancy occurring during participation in the OPTION-DM study will be reported on a pregnancy form within 24 hours of the Investigator being aware of the pregnancy.

Any pregnancy that occurs in a study participant will be followed up, with the permission of the participant, and the details recorded on the appropriate CRF. Study treatment will be discontinued as detailed in Section 8.11.

10.4 Study Centre/Investigator Responsibilities

All AEs and ARs, whether expected or not, will be recorded in the participant's medical notes and recorded in the toxicity (symptoms) section of the appropriate CRF. SAEs and SARs will be notified to the CTRU **within 24 hours** of the investigator becoming aware of the event.

10.4.1 Investigator/Study Nurse Assessment

Seriousness:
When an AE or AR occurs, the study nurse or investigator must assess whether the event is serious or not using the definitions in Table 6. Events assessed as serious will be reported as an SAE.

Severity (intensity):
The severity in this study will be assessed as follows:

- Mild – does not interfere with routine activities
- Moderate – interferes with routine activities
- Severe – prevents routine activities

Causality:
The study nurse or investigator must assess the causality in relation to study treatment for all AEs as per the definitions in the following table. Note that the causality assessment for events classed as serious must be completed by the investigator or a medically qualified member of staff who has been delegated this task:

Relationship	Description	Event Type
Unrelated	There is no evidence of any causal relationship. N.B. an alternative cause for the AE/SAE will be given.	AE/SAE
Unlikely	There is little evidence to suggest a causal relationship. There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant medication).	AE/SAE
Possible	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 medication).	AR/SAR
Probable	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.	AR/SAR
Definite	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.	AR/SAR
Not assessable	There is insufficient or contradictory information which cannot be supplemented or verified.	Treated as AR/SAR until relationship can be assessed

10.4.2 Notification of SAEs

CTRU will be notified of all SAEs, except those listed in section 10.2, within 24 hours of the investigator becoming aware of the event.

Investigators must notify CTRU of all SAEs occurring from the time of randomisation up until 30 days after the last administration of protocol treatment. SARs and SUSARs must be notified to CTRU until study closure.

10.5 SAE Notification Procedure

The SAE form must be completed by the investigator (a clinician named on the delegation log who is responsible for the participants care). In the absence of the investigator the form will be completed by a member of the study team and faxed as appropriate. The responsible investigator will subsequently check the SAE form, make changes as appropriate, sign and re-fax the form to CTRU as soon as possible.

Initial SAE reports must be followed by detailed reports when further information becomes available.

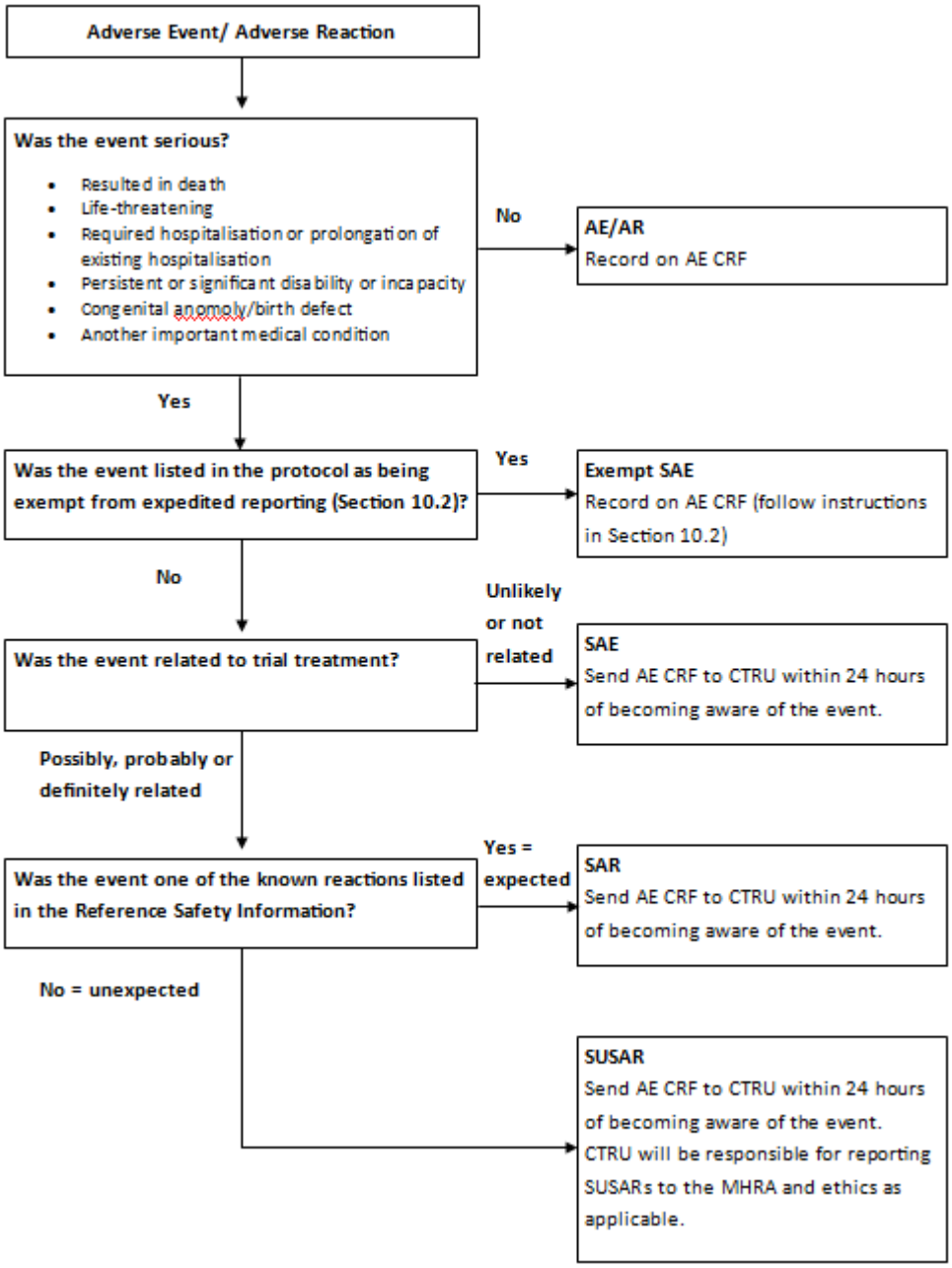
All SAE forms must be sent by fax to 0114 222 0870. Receipt of the initial report will be confirmed within one working day. Contact the study team at CTRU if confirmation of receipt is not received within one working day.

Concomitant medications are recorded throughout the study and will not be collected on AE/SAE forms as standard. However for any event classified as a SUSAR CTRU may request additional information on concomitant treatments to facilitate onward reporting.

Follow up: participants must be followed up until clinical recovery is complete and laboratory results have returned to normal or baseline, or until the event has stabilised. Follow up information will be provided on an SAE report marked as such.

Please refer to Figure 5 for further clarification on the SAE reporting procedure.

Figure 5: Procedure for AE/SAE reporting



10.6 CTRU Responsibilities

The Chief Investigator or delegate will be responsible for the assessment of expectedness. An unexpected adverse reaction is one not previously reported in the Reference Safety Information (RSI) of any of the Summary of Product Characteristics (SmPCs) used in the study or one that is more frequent or more severe than reported in the RSI. If a SAR is assessed as 'unexpected', it becomes a SUSAR.

The RSI to be used in the study will be section 4.8 of the SmPCs in the version which has been submitted to and approved by the MHRA for this trial.

The Sponsor has delegated CTRU responsibility for the reporting of SUSARs and other SARs to the regulatory authorities and the research ethics committee as appropriate. CTRU will also keep all investigators informed of any safety issues that arise during the course of the study.

11. Statistical Considerations

11.1 Study Hypothesis

The null hypothesis is that there is no difference between the study Treatment Pathways and the alternative hypothesis is that there is a true difference.

11.2 Analysis Sets

The following analysis sets will be used in the reporting of the study:

- **Safety population:** comprised of all participants who received at least one dose of study drug. The participants will be analysed based on Treatment Pathway they were receiving.
- **Intention-to-treat population (ITT):** comprised of all participants randomised regardless of drug intake. The participants will be analysed based on Treatment Pathways. Additionally modified ITT could be declared depending, for example, on withdrawal status and outcome availability.
- **Per-protocol population:** comprised of all participants randomised who took at least one dose of study drug and have no major protocol non-compliances. The participants will be analysed based on Treatment Pathways.

A TSC meeting will be held prior to unblinding, using clean data to review the protocol deviations and determine patients classified to the different populations.

11.3 Sample Size

A one point change in an individual on the NRS scale is considered a minimum clinically important difference (55). Hence, the proportion of people improving by at least one point would seem a suitable outcome. However we have based the sample size calculation on a continuous outcome, the mean change between groups, in order to maintain power (56). We have chosen a mean change between groups of 0.5 points based on the effect size previously reported for comparison of 2 active interventions for neuropathic pain in a crossover study (25). We estimate this would equate to an 8% difference between groups in the proportion of people improving by at least 1 point (57). Using a within patient SD of 1.65 (25), an alpha 0.0167 to allow for 3 comparisons, and 90% power we require 294 evaluable patients (58).

The plan was to screen 536 DPNP patients in total for participation in the study. Assuming a 25% drop out rate plan was to recruit and randomise 392 patients randomised to ensure 294 patients are expected to complete the study.

Due to difficulties with recruitment, the trial will stop recruiting in July 2019 when approximately 152 participants have been randomised. With the same assumption of an anticipated dropout rate of 25% drop out the expected evaluable sample size will be 114 patients completing the study.

The sample size is not now based on formal power calculations, but rather the size of difference which can be detected with the revised sample size. Using the original assumptions of a within patient SD of 1.65 (25), and an alpha 0.0167 to allow for 3 pairwise comparisons the study has 90% power to detect a difference of 0.81 points. Using a precision-based approach, the mean difference between any two trial arms will be estimated to within a standard error of 0.155 points.

11.4 Statistical Analysis

The statistical analysis will be reported according to CONSORT guidelines (59) and using an intention to treat approach as the primary analysis. As three comparisons will be performed, all statistical tests will be two-tailed at 1.67% significance level. The primary outcome and other continuous outcomes will be analysed using a random effects model with participant, treatment, sequence and period entered into the model. Participant will be entered as a random term. Contrasts will be used to evaluate the difference in means. Three 98.33% confidence intervals for the difference on treatment effect will be reported as well as the associated P value.

In case of missing data, the missing data mechanism will be explored and multiple imputation may be applied as a sensitivity analysis as appropriate. Other sensitivity analyses will be performed in order to evaluate the robustness of the primary analyses (60).

A logistic regression will be undertaken to analyse binary outcomes using a model similar to that for the continuous outcomes. Differences between treatment groups will be reported as odds ratios with associated 98.33% confidence intervals and P- values.

Further details will be provided in a separate statistical analysis plan.

12. Study supervision

Conduct of this study will be governed by three committees:

12.1 Trial Steering Committee (TSC)

A Trial Steering Committee (TSC) has been formed consisting of independent clinicians, an independent statistician and a PPI representative. The role of the TSC is to provide supervision of the protocol and statistical analysis plan, to provide advice on and monitor progress of the study, to review information from other sources and consider recommendations from the DMEC. The TSC will meet at regular intervals as outlined in the TSC terms of reference.

12.2 Data Monitoring and Ethics Committee (DMEC)

A Data Monitoring and Ethics Committee (DMEC) has been formed consisting of an independent statistician and two independent clinicians with clinical study expertise. The DMEC will review reports provided by the CTRU to assess the progress of the study, the safety data and the critical endpoint data as required. No formal interim analyses and stopping guidelines are set in advance. The DMEC meet 6-monthly and will make recommendations to the TSC as to the continuation of the study.

12.3 Trial Management Group (TMG)

The Trial Management Group (TMG) consists of the CI, other site PIs, collaborators and staff from CTRU. The CI will chair monthly meetings to discuss day-to-day implementation of the study.

13. Data handling and record keeping

Participant confidentiality will be respected at all times and the principles of the UK Data Protection Act (DPA) will be followed. The investigator will ensure that identifiable data is kept securely and protected from unauthorised parties.

Data management will be provided by the University of Sheffield Clinical Trials Research Unit (CTRU) who adhere to their own Standard Operating Procedures (SOPs) relating to all aspects of data management including data protection and archiving. A separate data management plan (DMP) will detail data management activities for the study in accordance with SOP (Shef/CTRU/DM009).

The investigator or delegate at each site will maintain comprehensive and accurate source documents to record all relevant study information regarding each participant. The CTRU will provide worksheets (shadow CRFs) to allow the site staff to check what is required for a visit. The worksheets do not need to be completed if alternative source documentation is provided. However, they must be completed for data points where source documentation is not collected elsewhere and where completed the worksheets must accurately reflect the database as they form part of the source data.

All participants will be assigned a unique study ID number at screening that will link all of the clinical information held about them on the study database. It will also be used in all correspondence between CTRU and participating centres.

Study records will be stored for 25 years after the completion of the study before being destroyed.

14. Data access and quality assurance

The study will use the CTRU's in-house data management system (Prospect) for the capture and storage of study specific participant data. Access to Prospect is controlled by usernames and encrypted passwords, and a comprehensive privilege management feature will be used to ensure that users have access to only the minimum amount of data required to complete their tasks. This can be used to restrict access to personal identifiable data.

A member of staff at each site will enter data from source documents into the study specific Prospect database when available. After data have been entered, electronic validation rules are applied to the database on a regular basis; discrepancies are tracked and resolved through the Prospect database. All entries and corrections are logged with the person, date and time captured within the electronic audit trail.

Participant confidentiality will be respected at all times. Participant names and contact details will be collected and entered on the database. Access to these personal details will be restricted to users with appropriate privileges. All other data will be anonymised and will only be identifiable by participant ID number, and no patient identifiable data will be transferred from the database to the statistician.

Participating investigators shall agree to allow study-related monitoring, including audits, ethics committee review and regulatory inspections by providing direct access to source data and documents as required. Participants' consent for this must be obtained.

14.1 Risk Assessment

Central, site and pharmacy monitoring will be undertaken at a level appropriate to a detailed risk assessment performed by the Sponsor and CTRU and in accordance with Sheffield CTRU Standard Operating Procedures. The level of risk will be agreed with the Sponsor.

14.2 On-site Monitoring

On-site monitoring will be performed according to the OPTION-DM Monitoring Plan and in line with the Sheffield CTRU Study Monitoring SOP.

An initiation visit will be performed before the first participant is included in the study. During this visit, the monitor will review with site staff the protocol, study requirements and their responsibilities to satisfy regulatory, ethical and sponsor requirements.

Regular site monitoring visits will occur throughout the study and additional visits will be undertaken where required. At these visits, the monitor will review activity to verify that the:

1. Data are authentic, accurate and complete,
2. Safety and rights of the patient are being protected and
3. Study is conducted in accordance with the approved protocol and study agreements, GCP and all applicable regulatory requirements.

Accurate and reliable data collection will be assured by verification and cross -check of the CRFs against investigator's records by the study monitor (source document verification). Any data recorded directly onto CRFs (i.e. no prior written or electronic record of data), may be considered source data. Study monitor will contact and visit sites regularly to inspect CRFs throughout the study, to verify adherence to the protocol and the completeness, consistency and accuracy of the data being entered on the CRFs. Monitoring visits will also include a pharmacy visit to review processes, documentation and accountability of study drug.

A close-out visit will be performed after study closure.

14.3 Central Monitoring at CTRU

CTRU staff will review entered data for possible errors and missing data points. A central review of consent forms will also be completed and sites will be requested to post consent forms to CTRU on an ongoing basis. CTRU will review pharmacy dispensing logs for some patients centrally. Details will be included in the pharmacy manual.

15. Publication

Results of the study will be disseminated in peer reviewed scientific journals and clinical and academic conferences.

Details of the study will also be made available on the SCHARR website. Summaries of the research will be updated periodically to inform readers of the ongoing progress.

Full details will be documented in the OPTION-DM Publication and Dissemination Plan.

16. Finance

OPTION-DM is funded by the UK NIHR Health Technology Assessment (HTA) Programme (project number 15/35/03) and details have been drawn up in a separate agreement. The views expressed are those of the author(s) and not necessarily those of NIHR or the Department of Health and Social Care. Participants can be reimbursed for the cost of reasonable travel expenses. Further details are included in the site agreement.

17. Ethics approval

Before initiation of the study at clinical sites, the protocol, all informed consent forms, and information materials to be given to the participants will be submitted to an ethics committee for approval. Any further amendments will be submitted and approved by the ethics committee.

In addition, the study will be submitted for HRA review and approval. Recruitment of study participants will not commence until the letter of approval has been received from the HRA.

18. Regulatory approval

The study will be conducted in accordance with the UK Clinical Trials Regulations 2004 and as such will be submitted to the Medicines and Healthcare Regulatory Agency (MHRA) for review. The study will not commence recruitment until a Clinical Trial Authorisation (CTA) has been granted by the MHRA.

19. Indemnity / Compensation / Insurance

Both the Sponsor (Sheffield Teaching Hospitals) and the University of Sheffield has in place insurance against liabilities for which it may be legally liable and this cover includes any such liabilities arising out of this clinical study.

NHS indemnity operates in respect of the clinical treatment which is provided.

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