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 2.0 7th Dec 2016

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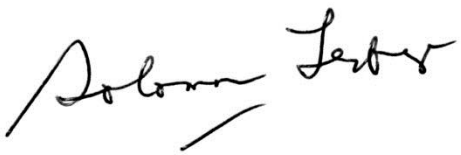
EudraCT	2016-003146-89

Authorised by: Professor Solomon Tesfaye
Chief Investigator



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
TCSS	Toronto Clinical Scoring System
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:

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Professor Blair Smith	Consultant in Pain Medicine, Ninewells Hospital
Professor Frances Game	Consultant Diabetologist, Derby Teaching Hospitals
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

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
Oxford University Hospitals NHS Foundation Trust
Nottingham University Hospitals NHS Trust
Poole Hospital NHS Foundation Trust
Tameside Hospital NHS Foundation Trust
Ipswich Hospital NHS Trust
Kings College Hospital NHS Foundation Trust
Lancashire Teaching Hospitals NHS Foundation Trust

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 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

<table>
<tr><td>Study Title:</td><td>Optimal Pathway for Treating neurOpathIc paiN in Diabetes Mellitus (OPTION-DM)</td></tr>
<tr><td>EudraCT:</td><td>2016-003146-89</td></tr>
<tr><td>Sponsor:</td><td>Sheffield Teaching Hospitals</td></tr>
<tr><td>Funder:</td><td>NIHR HTA (project number 15/35/03)</td></tr>
<tr><td>Project start date:</td><td>1st June 2016</td></tr>
<tr><td>Project end date:</td><td>31st August 2019</td></tr>
<tr><td>Study Design:</td><td>Multicentre, double-blind, 3x3 Williams Square crossover trial.</td></tr>
<tr><td>Participants:</td><td>392 participants with Diabetic Peripheral Neuropathic Pain (DPNP).</td></tr>
<tr><td>Setting:</td><td>Participants will be recruited from 8 secondary care DPNP centres and 80 primary care practices.</td></tr>
<tr><td>Interventions:</td><td>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 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</td></tr>
</table>

	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.

Figure 1: Patient flow chart

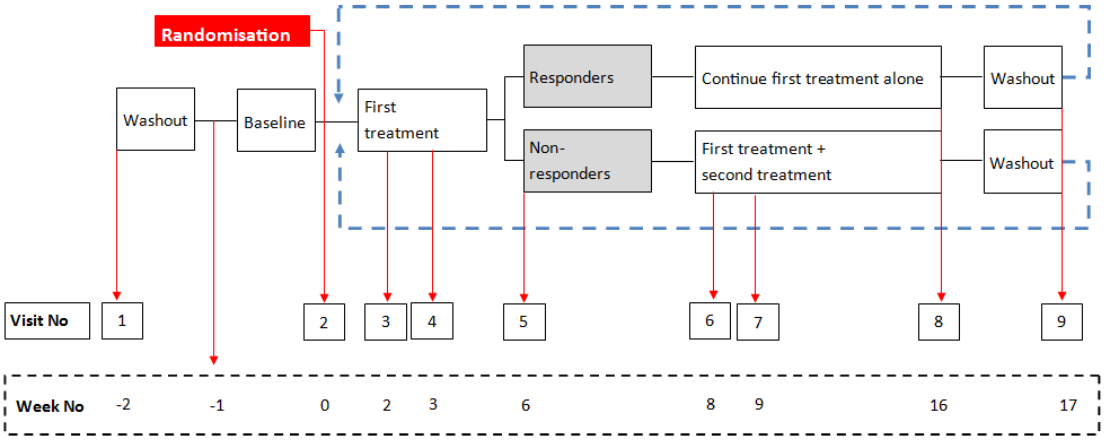


Figure 2: Dosing and titration schedule for each treatment pathway. Participants continue on maintenance dose of drug from the First Treatment Phase for the duration of the Second Treatment Phase.

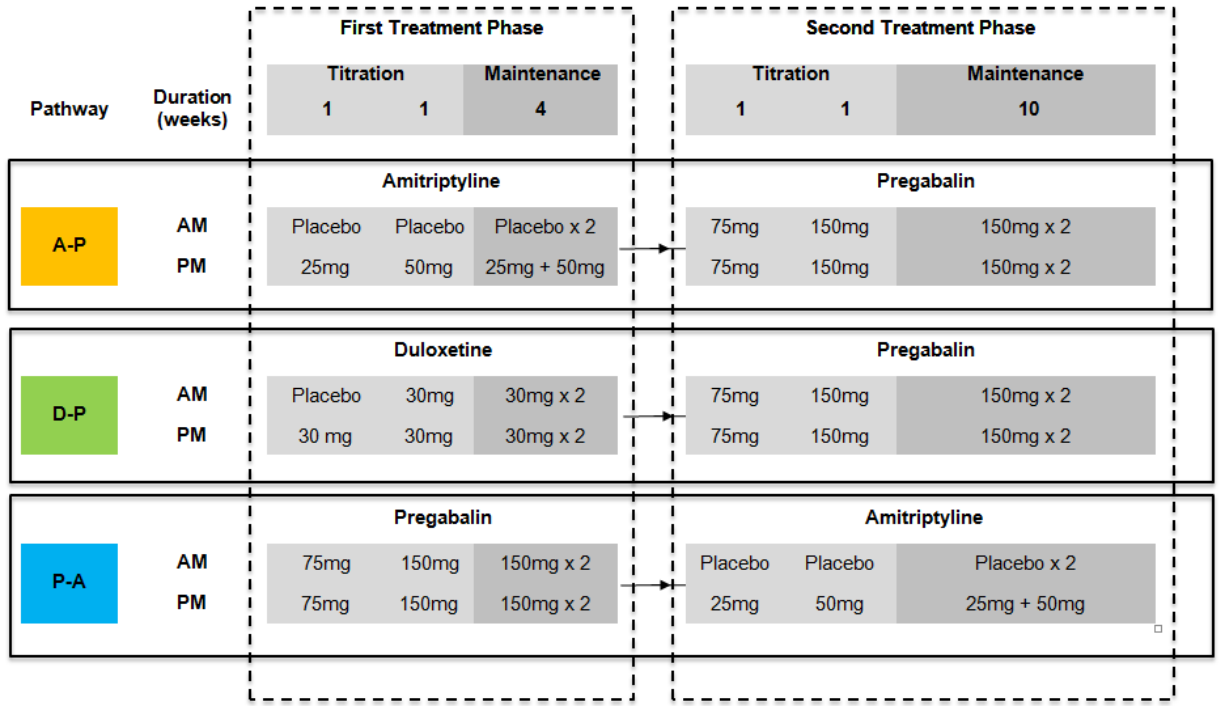
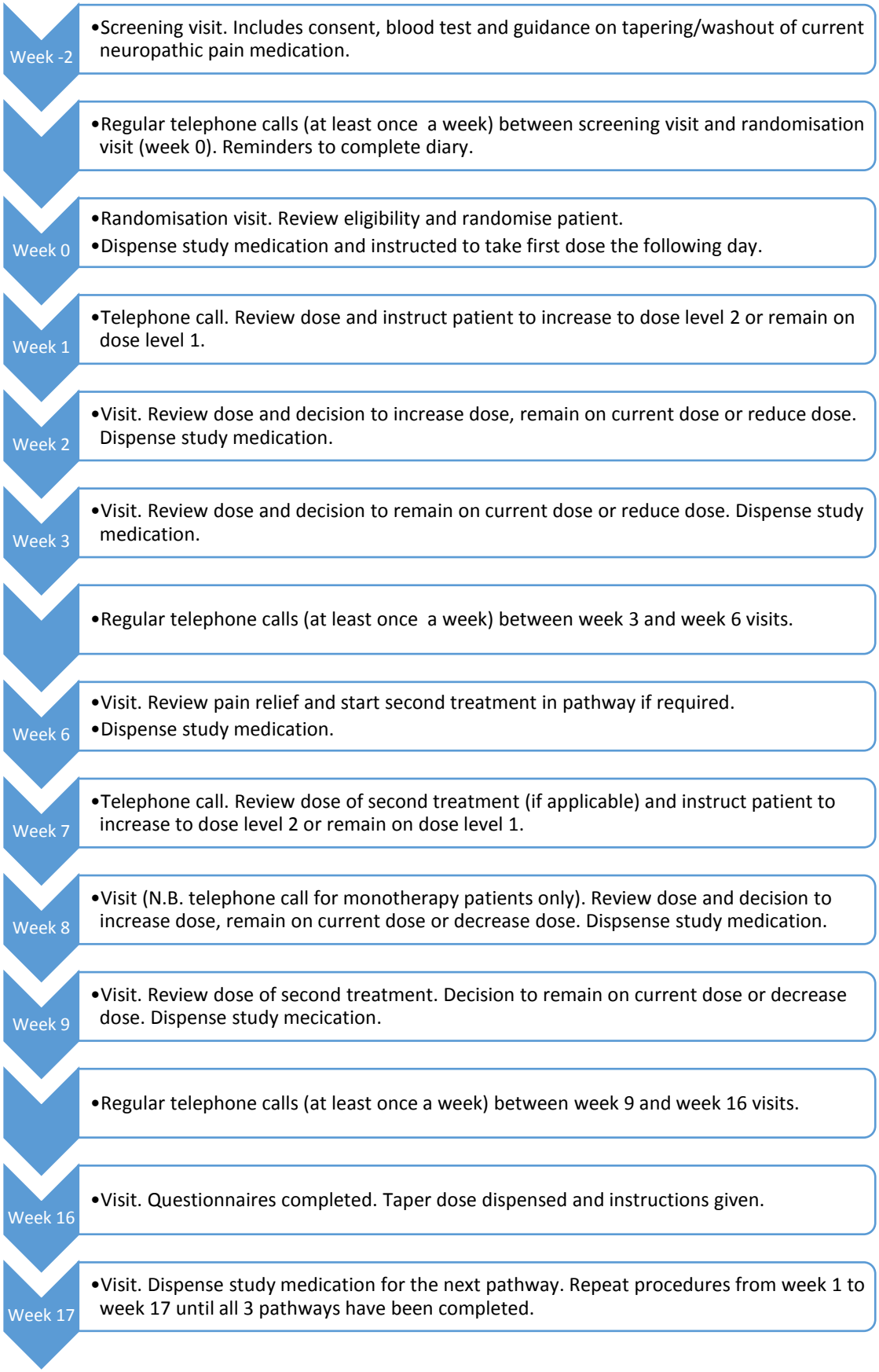


Figure 3: Patient visits during each pathway.



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 6 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. During month 16 the Study 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.

4.3 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).

4.4 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. The score will be standardised against English population reference (39).
3. Difference between RAND SF-36 physical mean scores (evaluated at patient level) at week 6 among pathways. The score will be standardised against English population reference (39).
4. Difference between RAND SF-36 mental mean scores (evaluated at patient level) at week 16 among pathways. The score will be standardised against English population reference (39).
5. Difference between RAND SF-36 mental mean scores (evaluated at patient level) at week 6 among pathways. The score will be standardised against English population reference (39).
6. Difference between Hospital Anxiety and Depression Scale (HADS) mean scores (evaluated at patient level) at week 6 among pathways. [40]
7. Difference between Hospital Anxiety and Depression Scale (HADS) mean scores (evaluated at patient level) at week 16 among pathways. [40]
8. 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.
9. 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.
10. Difference in BPI-MSF measure of pain interference with function total score (evaluated at patient level) at week 6 among pathways (40).
11. Difference in BPI-MSF measure of pain interference with function total score (evaluated at patient level) at week 16 among pathways (40).
12. Difference in Insomnia Severity Index (evaluated at patient level) total score at week 6 among pathways.
13. Difference in Insomnia Severity Index (evaluated at patient level) total score at week 16 among pathways.
14. Difference in Patient Global Impression of Change (evaluated at patient level) at week 16 among pathways (41).
15. Difference in proportion of care pathway preferred by participants at week 50.

Cost Effectiveness

16. 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 (42).
17. 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 (43).

Safety

18. 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).

19. Frequency and proportion of Adverse Events for each of the pathway.
20. Listing of Adverse Events for each of the pathway.
21. Frequency and proportion of patients reporting at least one Serious Adverse Event for each of the pathway. 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.
22. Frequencies of Serious Adverse Events for each of the pathway.
23. Listing of Serious Adverse Events for each of the pathway.

Subgroup

Neuropathic Pain Symptom Inventory (NPSI) questionnaire for subgroup analysis relating pain phenotype to treatment response (44). There is emerging evidence that treatment response may be determined by a patient's pain phenotype (45–47). In particular these outcomes will be evaluated:

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

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) (48). 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 (42).

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) (49).

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 will be frozen and stored locally study 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.

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.

6.2 Inclusion Criteria

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

1. Participant aged ≥18 years
2. Daily pain for at least 3 months or taking pain medication for neuropathic pain for at least 3 months.
3. Bilateral distal symmetrical polyneuropathy confirmed by Toronto Clinical Scoring System (TCSS) score > 5 at screening visit (50)
4. Bilateral distal symmetrical polyneuropathy confirmed by the Douleur Neuropathique 4 (DN4) questionnaire at screening visit (51)
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)
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 neuropathies
2. History of alcohol/substance abuse
3. History of severe psychiatric illnesses
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
8. Use of high dose morphine equivalent (>120mg/day)
9. Liver disease (LFTs >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 II
12. Clinically significant cardiac arrhythmias on 12 lead ECG
13. Prior history of ischaemic heart disease
14. Postural hypotension (reduction of > 20mmHg)
15. Prostatic hypertrophy or urinary retention
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

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.

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)
- Ethnicity
- Suicidal risk questionnaire (self-completed or administered by the study team)
- Review of concomitant medications

- A full physical and neurological assessment to ensure the presence of a distal symmetrical polyneuropathy that starts in the feet
- TCSS 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
- Glycosylated haemoglobin A1c
- 12 lead ECG

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 4 days. If the participant is on combination therapy then all drugs will be tapered at once. They 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.

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.

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
- Vital signs (heart rate and blood pressure [lying and standing])
- Neuropathic pain assessment:
    - Pain diaries will be checked to confirm participants ' eligibility (mean NRS pain score >3)
    - 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
    - Patient Global Impression of Change (PGIC)
    - Modified health resource questionnaire based on Client Service Receipt Inventory (CSRI) to capture health resources used.

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 the following morning. New diaries will be provided and participants reminded to complete 24-hour average pain scores daily throughout the study.

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 observational 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 the end 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. 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. In this instance, the same protocol schedule will still be followed i.e. it is not possible to start a new pathway early.

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.

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.

Table 1: Dosing schedule by dose level

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

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.

During the first 2 weeks of each treatment phase, the dose will be escalated towards the maximum tolerated dose or maximum permitted dose, whichever is first, (see Figure 2) based on treatment response (based on the 24-hour pain NRS score) and side effect profile.

During the weekly telephone calls, 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 does not need to be increased further. Patients will also be asked to rate any reported side effects. These will be graded (mild, moderate or severe) and whether side effects are tolerable or intolerable. Any moderate or severe or intolerable side effects will require a medication review (i.e. consider dose reduction or discontinuation).

In case of significant intolerability, based on investigator and participant decision, the dose will be reduced by one dose level. Detailed guidance on the dose titration phase will be provided in a study-specific SOP.

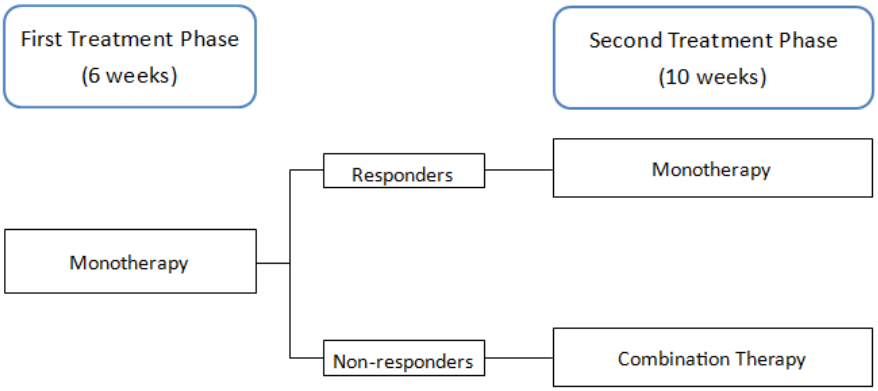
In the third week of each treatment phase, each participant will receive his or her maximal tolerated dose for the particular treatment. At the end of each treatment pathway, participants will undergo three days of dose tapering and four days of complete washout.

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 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.

At the week 6 follow-up visit a decision will be taken to either continue on monotherapy or to add combination therapy 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 (52).

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 a second agent 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.

8.3.3 Switching Treatment during a Pathway

At the week 6 visit, if there was no change in pain scores from baseline participants will switch to the second drug in the Treatment Pathway.

If there is significant intolerance to monotherapy, participants can switch to the second drug in the Treatment Pathway. In this situation the switch can be made immediately, at any time, without the need to washout the first treatment. The second drug 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 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 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 Dispensing and Accountability Log.

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 during the titration phase.

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 first be discussed with CTRU. 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, unblinding can be performed via an access controlled system available on the OPTION-DM website (http://www.sheffield.ac.uk/scharr/sections/dts/ctru/option-dm).

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 be unblinded and will be responsible for reporting any Suspected Unexpected Serious Adverse Reactions (SUSARs) as appropriate. In the event that this individual is unavailable, a delegated member of staff at CTRU will perform the unblinding in order that the event can be reported appropriately.

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)
- Other neuropathic pain medications (e.g. venlafaxine, IV lignocaine etc.)
- Use of any medications that could lead to potentially serious interactions with study medications

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 an effective contraception. If a participant becomes pregnant during the study, the study treatment will be discontinued and an SAE form completed. The participant will remain in the study for follow up as detailed in Section 6.6.

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 the week 2 visit onwards until all 3 pathways are complete.

Assessments		Weeks from starting treatment pathway[a]							
	-2[a, b]	0[c]	2[c]	3[c]	6[c]	8[c,d]	9[c]	16[c, e]	17[f]
Blood Tests[g]	X[h]							X	
ECG	X								
Medical History	X								
Physical and neurological assessment	X								
Toronto Clinical Scoring System (TCSS)	X								
Douleur Neuropathique 4 (DN4)	X								
Suicidal risk questionnaire	X								
Concomitant Medications	X	X	X	X	X	X	X	X	X
Dispense Study Medication		X	X	X	X	X	X	X	X
Pain Diaries[i]		X	X	X	X	X	X	X	X
Brief Pain Inventory-Modified Short Form (BPI-MSF)		X			X			X	
Insomnia Severity Index (ISI)		X			X			X	
Neuropathy Pain Symptom Inventory (NPSI)		X			X			X	
Hospital Anxiety and Depression Scale (HADS)		X			X			X	
RAND Short Form 36 (RAND SF-36)		X			X			X	
EQ-5D-5L		X			X			X	
Client Service Receipt Inventory (CSRI)		X			X			X	
Pain Catastrophising Scale (PCS)		X							
Vital Signs[j]		X						X	
Adverse Events Assessment			X	X	X	X	X	X	X
Compliance Assessment			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 be within +/- 2 days of the scheduled visit date. Scheduled visit dates relate to the date of the previous visit.
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).
f. At week 17, following the washout, the participant will begin first line treatment on the next treatment pathway and the visits from week 2 to week 17 will be repeated until all 3 pathways have been completed.
g. FBC, urea and electrolytes, liver function tests, glycosylated haemoglobin A1c.
h. Whole blood sample to be collected and stored for future research. Please refer to the OPTION-DM Sample Collection Manual for details.
i. To be completed by participants daily during the study, starting during the baseline period.
j. Heart rate and blood pressure (lying and standing).

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 on page 25.

- Blood tests will be performed at week 16
- Vital signs will be assessed at week 0 and week 16
- 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 on page 25 to assess neuropathic pain:

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

Questionnaires will 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)

Questionnaires will 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 study will end after the last follow-up visit of the last study participant. Sites will be closed once data cleaning is completed and the regulatory authority and ethics committee informed.

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 2 below.

Table 2: 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 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. Pregnancy occurring during participation in the OPTION-DM study will be reported on an SAE 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 2. 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 and ARs 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.	Not assessable

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.

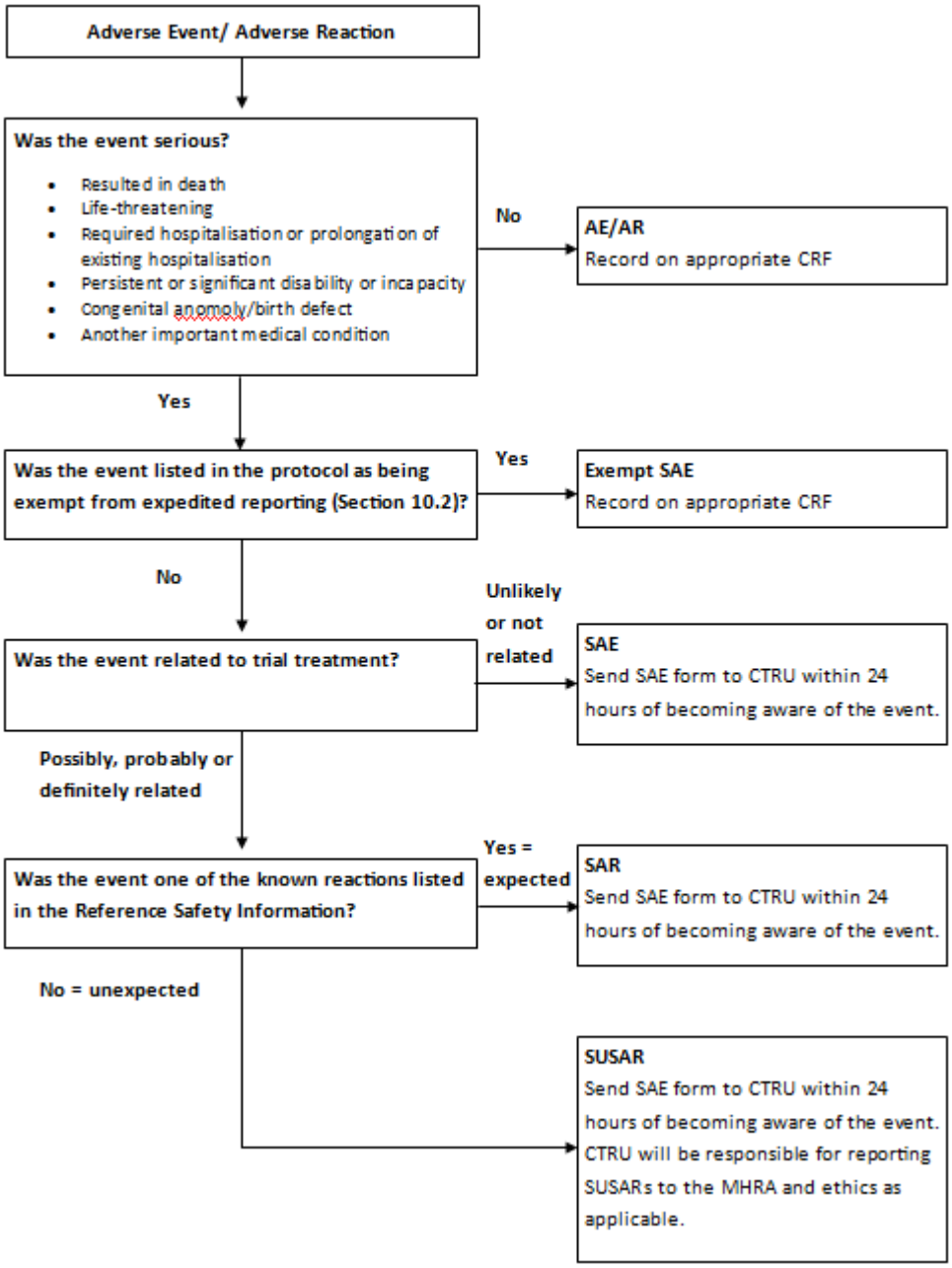
All SAE forms must be sent by fax to 0114 222 0870. Receipt of the initial report will be confirmed within one working day. Contact the study team at CTRU if confirmation of receipt is not received within one working day.

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 deviations. 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 (53). 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 (54). 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 (55). 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 (56).

536 DPNP patients in total will be screened for participation in the study. Assuming a 25% drop out rate 392 patients will be randomised to ensure 294 patients are expected to complete the study.

11.4 Statistical Analysis

The statistical analysis will be reported according to CONSORT guidelines (57) 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 (58).

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 Study Steering Committee (TSC)

A Study 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 Study Management Group (TMG)

The Study 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).

Participants will not be identified on CRFs or study database by their names. All participants will be assigned a unique study ID number at randomisation 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 participant data. Access to Prospect is controlled by usernames and encrypted passwords, and a comprehensive privilege management feature can 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.

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. 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.

20. References

1. Abbott C, Malik R, Van Ross ERE, Kulkarni J, Boulton AJM. Prevalence and characteristics of painful diabetic neuropathy in a large community-based diabetic population in the U.K. Diabetes Care. 2011;34(10):2220–4.

2. Davies M, Brophy S, Williams R, Taylor A. The prevalence, severity, and impact of painful diabetic peripheral neuropathy in type 2 diabetes. Diabetes Care. 2006;29(7):1518–22.

3. Veves A, Backonja M, Malik R. Painful diabetic neuropathy: Epidemiology, natural history, early diagnosis, and treatment options. Pain Med. 2008;9(6):660–74.

4. Boulton A, Vinik A, Arezzo J. Diabetic neuropathies: a statement by the American Diabetes Association. Diabetes Care. 2005;28(4):956–62.

5. Galer BS, Gianas A, Jensen MP. Painful diabetic polyneuropathy: Epidemiology, pain description, and quality of life. Diabetes Res Clin Pract. 2000;47(2):123–8.

6. Zelman DC, Brandenburg N, Gore M. Sleep impairment in patients with painful diabetic peripheral neuropathy. Clin J Pain. 2006;22(8):681–5.

7. Gore M, Brandenburg N, Dukes E, Hoffman DL, Tai KS, Stacey B. Pain severity in diabetic peripheral neuropathy is associated with patient functioning, symptom levels of anxiety and depression, and sleep. J Pain Symptom Manage. 2005;30(4):374–85.

8. Gore M, Brandenburg N, Hoffman D, Tai K-S, Stacey B. Burden of Illness in Painful Diabetic Peripheral Neuropathy: The Patients' Perspectives. J Pain. 2006;7(12):892–900.

9. Tolle T, Xu X, Sadosky AB. Painful diabetic neuropathy: A cross-sectional survey of health state impairment and treatment patterns. J Diabetes Complications. 2006;20(1):26–33.

10. National Institute for Health and Care Excellence. Neuropathic pain in adults: pharmacological management in non-specialist settings. NICE Clin Guidel. 2013;(November 2013).

11. Moore R, Derry S, Aldington D, Cole P, Wiffen PJ. Amitriptyline for neuropathic pain in adults. Cochrane database Syst Rev. 2015;7(7):CD008242.

12. Lunn M, Hughes R, Wiffen P. Duloxetine for treating painful neuropathy , chronic pain or fibromyalgia (Review). Cochrane Database Syst Rev. 2014;(1).

13. Moore R, Straube S, Wiffen PJ, Derry S, McQuay HJ. Pregabalin for acute and chronic pain in adults. CochraneDatabaseSystRev. 2009;(3):CD007076.

14. Moore R, Wiffen P, Derry S, Mcquay H. Gabapentin for chronic neuropathic pain and fibromyalgia in adults (Review). CochraneDatabaseSystRev. 2011;(3).

15. Freeman R, Durso-DeCruz E, Emir B. Efficacy, safety, and tolerability of pregabalin treatment for painful diabetic peripheral neuropathy: Findings from seven randomized, controlled trials across a range of doses. Diabetes Care. 2008;31(7):1448–54.

16. Sultan A, Gaskell H, Derry S, Moore RA. Duloxetine for painful diabetic neuropathy and fibromyalgia pain: systematic review of randomised trials. BMC Neurol. 2008;8(1):29.

17. Wong M, Chung JWY, Wong TKS. Effects of treatments for symptoms of painful diabetic neuropathy: systematic review. BMJ. 2007;335(7610):87.

18. Tesfaye S, Vileikyte L, Rayman G, Sindrup S, Perkins B, Baconja M, et al. Painful diabetic peripheral neuropathy: consensus recommendations on diagnosis, assessment and management. Diabetes Metab Res Rev. 2011;27:629–38.

19. Dworkin R, O'Connor A, Audette J, Baron R, Gourlay G, Haanpaa M, et al. Recommendations for the pharmacological management of neuropathic pain: An overview and literature update. Mayo Clin Proc. 2010;85(3 Suppl):S3–14.

20. Attal N, Cruccu G, Baron R, Haanpaa M, Hansson P, Jensen TS, et al. EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. Eur J Neurol. 2010;17(9):1113–23.

21. Bansal D, Bhansali A, Hota D, Chakrabarti A, Dutta P. Amitriptyline vs. pregabalin in painful diabetic neuropathy: A randomized double blind clinical trial. Diabet Med. 2009;26(10):1019–26.

22. Kaur H, Hota D, Bhansali A, Dutta P, Bansal D, Chakrabarti A. A comparative evaluation of amitriptyline and duloxetine in painful diabetic neuropathy: A randomized, double-blind, cross-over clinical trial. Diabetes Care. 2011;34(4):818–22.

23. Boyle J, Eriksson MEV, Gribble L, Gouni R, Johnsen S, Coppini D V., et al. Randomized, Placebo-Controlled Comparison of Amitriptyline, Duloxetine, and Pregabalin in Patients With Chronic Diabetic Peripheral Neuropathic Pain. Diabetes Care. 2012;35(12):2451–8.

24. Quilici S, Chancellor J, Löthgren M, Simon D, Said G, Le TK, et al. Meta-analysis of duloxetine vs. pregabalin and gabapentin in the treatment of diabetic peripheral neuropathic pain. BMC Neurol. 2009;9(1):6.

25. Gilron I, Bailey JM, Tu D, Holden RR, Weaver DF, Houlden RL. Morphine, Gabapentin, or Their Combination for Neuropathic Pain. N Engl J Med. 2005;352(13):1324–34.

26. Tesfaye S, Selvarajah D. Morphine, gabapentin, or their combination for neuropathic pain. N Engl J Med. 2005;352(25):2650–1.

27. Tesfaye S, Wilhelm S, Lledo A, Schacht A, Tölle T, Bouhassira D, et al. Duloxetine and pregabalin: High-dose monotherapy or their combination? the “COMBO-DN study” - A multinational, randomized, double-blind, parallel-group study in patients with diabetic peripheral neuropathic pain. Pain. 2013;154(12):2616–25.

28. Wu EQ, Birnbaum HG, Mareva MN, Le TK, Robinson RL, Rosen A, et al. Cost-effectiveness of duloxetine versus routine treatment for U.S. patients with diabetic peripheral neuropathic pain. J Pain. 2006;7(6):399–407.

29. Beard SM, McCrink L, Le TK, Garcia-Cebrian A, Monz B, Malik R. Cost effectiveness of duloxetine in the treatment of diabetic peripheral neuropathic pain in the UK. Curr Med Res Opin. 2008;24(2):385–99.

30. O’Connor A, Noyes K, Holloway R. A cost utility comparison of four first line medications in painful diabetic neuropathy . 2016;26(12):1–2.

31. Javed S, Petropoulos IN, Alam U, Malik R. Treatment of painful diabetic neuropathy. Ther Adv Chronic Dis. 2014;6(1):15–28.

32. Vinik A, Rosenstock J, Sharma U, Feins K, Hsu C, Merante D. Efficacy and safety of mirogabalin (DS-5565) for the treatment of diabetic peripheral neuropathic pain: A randomized, double-blind, placebo- and active comparator-controlled, adaptive proof-of-concept phase 2 study. Diabetes Care. 2014;37(12):3253–61.

33. Selvarajah D, Cash T, Sankar A, Thomas L, Davies J, Cachia E, et al. The contributors of emotional distress in painful diabetic neuropathy. Diabetes Vasc Dis Res. 2014;11(4):218–25.

34. Gordois A, Scuffham P, Shearer A, Oglesby A, Tobian J. The Health Care Costs of Diabetic Peripheral Neuropathy in the US. Diabetes Care. 2003;26:1790–5.

35. Ritzwoller DP, Ellis JL, Korner EJ, Hartsfield CL, Sadosky A. Comorbidities, healthcare service utilization and costs for patients identified with painful DPN in a managed-care setting. Curr Med Res Opin. 2009;25(6):1319–28.

36. Drug Cost Data from Sheffield CCG, Personal communication. 2015.

37. Backonja M, Beydoun A, Edwards K, Schwartz S, Fonseca V, Hes M, et al. Gabapentin for the Symptomatic Treatment of Painful Neuropathy in Patients With Diabetes Mellitus A Randomized Controlled Trial. 1998;280(21):1831–6.

38. Dworkin RH, Turk DC, Peirce-Sandner S, Burke LB, Farrar JT, Gilron I, et al. Considerations for improving assay sensitivity in chronic pain clinical trials: IMMPACT recommendations. Pain. International Association for the Study of Pain; 2012;153(6):1148–58.

39. Jenkinson C, Coulter A, Wright L. Short form 36 (SF36) health survey questionnaire: Normative data for adults of working age. BMJ. 1993;306(SF 36):1437–40.

40. Cleeland CS, Ryan KM. Pain assessment: global use of the brief pain inventory. Ann Acad Med Singapore. 1994;23(2):129–38.

41. Guy W. ECDEU assessment manual for psychopharmacology. Rockville, MD - Natl Inst Ment Heal Psychopharmacol Res Branch. 1976;217–22, 313–31, 534–7.

42. Devlin N, Shah K, Feng Y, Mulhern B, Hout B Van. Valuing health-related quality of life : An EQ-5D-5L value set for England. 2016;(January).

43. Beecham J, Knapp M. Costing Psychiatric Interventions. Measuring Mental Health Needs. 2001. p. 200–24.

44. Bouhassira D, Attal N, Fermanian J, Alchaar H, Gautron M, Masquelier E, et al. Development and validation of the Neuropathic Pain Symptom Inventory. Pain. 2004;108(3):248–57.

45. Demant D, Lund K, Vollert J, Maier C, Segerdahl M, Finnerup N, et al. The effect of oxcarbazepine in peripheral neuropathic pain depends on pain phenotype: a randomised, double blind, placebo-controlled phenotype-stratified study. Pain. 2014;155(11):2263–73.

46. Bouhassira D, Wilhelm S, Schacht A, Perrot S, Kosek E, Cruccu G, et al. Neuropathic pain phenotyping as a predictor of treatment response in painful diabetic neuropathy: Data from the randomized, double-blind, COMBO-DN study. Pain. International Association for the Study of Pain; 2014;155(10):2171–9.

47. Marchettini P, Wilhelm S, Petto H, Tesfaye S, Tölle T, Bouhassira D, et al. Are there different predictors of analgesic response between antidepressants and anticonvulsants in painful diabetic neuropathy? Eur J Pain (United Kingdom). 2016;20(3):472–82.

48. National Institute for Health and Care Excellence. Guide to the Methods of Technology Appraisal. 2007;(November).

49. Glick H, Doshi J, Sonnad S, Polsky D. Economic evaluation in clinical trials. 2014.

50. Bril V, Perkins B a. Validation of the Toronto clinical scoring system for diabetic polyneuropathy. Diabetes Care. 2002;25(11):2048–52.

51. Bouhassira D, Attal N, Alchaar H, Boureau F, Brochet B, Bruxelle J, et al. Comparison of pain syndromes associated with nervous or somatic lesions and development of a new neuropathic pain diagnostic questionnaire (DN4). Pain. 2005;114(1-2):29–36.

52. Zelman DC, Dukes E, Brandenburg N, Bostrom A, Gore M. Identification of cut-points for mild, moderate and severe pain due to diabetic peripheral neuropathy. Pain. 2005;115(1-2):29–36.

53. Dworkin RH, Turk DC, Wyrwich KW, Beaton D, Cleeland CS, Farrar JT, et al. Interpreting the Clinical Importance of Treatment Outcomes in Chronic Pain Clinical Trials: IMMPACT Recommendations. J Pain. 2008;9(2):105–21.

54. Senn S, Julious S. Measurement in clinical trials: A neglected issue for statisticians? Stat Med. 2009;28(26):3189–209.

55. Julious S, Walters SJ. Estimating effect sizes for health-related quality of life outcomes. Stat Methods Med Res. 2014;23(5):430–9.

56. Julious S. Tutorial in biostatistics: Sample sizes for clinical trials with Normal data. Stat Med. 2004;23(12):1921–86.

57. Moher D, Hopewell S, Schulz KF, Montori V, Gotzsche PC, Devereaux PJ, et al. CONSORT 2010 explanation and elaboration: Updated guidelines for reporting parallel group randomised trials. Int J Surg. 2012;10(1):28–55.

58. Thabane L, Mbuagbaw L, Zhang S, Samaan Z, Marcucci M, Ye C, et al. A tutorial on sensitivity analyses in clinical trials: the what, why, when and how. BMC Med Res Methodol. BMC Medical Research Methodology; 2013;13(1):92.