



STUDY PROTOCOL

DOLORisk: study protocol for a multi-centre observational study to understand the risk factors and determinants of neuropathic pain [version 1; referees: 1 approved, 1 approved with reservations]

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Abstract

Background: Neuropathic pain is an increasingly prevalent condition and has a major impact on health and quality of life. However, the risk factors for the development and maintenance of neuropathic pain are poorly understood. Clinical, genetic and psychosocial factors all contribute to chronic pain, but their interactions have not been studied in large cohorts. The DOLORisk study aims to study these factors.

Protocol: Multicentre cross-sectional and longitudinal cohorts covering the

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Invited Referees

main causes leading to neuropathic pain (e.g. diabetes, surgery, chemotherapy, traumatic injury), as well as rare conditions, follow a common protocol for phenotyping of the participants. This core protocol correlates answers given by the participants on a set of questionnaires with the results of their genetic analyses. A smaller number of participants undergo deeper phenotyping procedures, including neurological examination, nerve conduction studies, threshold tracking, quantitative sensory testing, conditioned pain modulation and electroencephalography.

Ethics and dissemination: All studies have been approved by their regional ethics committees as required by national law. Results are disseminated through the [DOLORisk website](#), scientific meetings, open-access publications, and in partnership with patient organisations.

Strengths and limitations:

- Large cohorts covering many possible triggers for neuropathic pain
- Multi-disciplinary approach to study the interaction of clinical, psychosocial and genetic risk factors
- High comparability of the data across centres thanks to harmonised protocols
- One limitation is that the length of the questionnaires might reduce the response rate and quality of responses of participants

Keywords

pain, neuropathy, neuropathic pain, diabetes, nerve injury, risk factors, protocol

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Competing interests: DLB has acted as a consultant on behalf of Oxford Innovation for Abide, Biogen, GSK, Lilly, Mitsubishi Tanabe, Mundipharma and TEVA over the last 3 years. NA received speaker honoraria from Pfizer and reported fees for consultant services from Novartis, Teva, Grünenthal, Mundipharma, Sanofi Pasteur, Aptinyx. ASCR has received funding from Orion Pharma. ASCR undertakes consultancy and advisory board work for Imperial College Consultants—in the past 12 months, this has included remunerated work for: Merck, Galapagos, Toray, Quartet, Lateral, Novartis and Orion. ASCR was the owner of share options in Spinifex Pharmaceuticals from which personal benefit accrued on the acquisition of Spinifex by Novartis in July 2015 and from which future milestone payments may occur. ASCR is named as an inventor on patents: Rice A.S.C., Vandevoorde S. and Lambert D.M Methods using N-(2-propenyl)hexadecanamide and related amides to relieve pain, WO 2005/079771 (Google Patents); Okuse K. et al Methods of treating pain by inhibition of vgf activity, EP13702262.0/WO2013 110945 (Google Patents).

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Introduction

Neuropathic pain affects 7–10% of the general population¹ and has a major impact on physical health, psychological health and quality of life². The response to analgesic treatment is often inadequate with only 40–60% of patients achieving partial relief, often at the cost of adverse effects³. The prevalence of neuropathic pain will increase due to the increasing prevalence of predisposing conditions, such as diabetes mellitus, and ageing, which is associated with neuropathic pain¹. There is an urgent clinical need to translate an increased preclinical level of understanding of neuropathic into clinical practice. In particular we need to understand the pathophysiology of neuropathic pain in clinical cohorts.

Neuropathic pain arises as a consequence of a disease or lesion in the somatosensory nervous system⁴. However, not all patients with such a lesion develop neuropathic pain. We do not understand why only a sub-group of patients with the same disease or neurological lesion develop neuropathic pain. The severity and impact of neuropathic pain vary between individuals with similar conditions⁵ and are unpredictable. A plausible explanation for the variation in neuropathic pain prevalence and severity is a complex interaction between genetic, psychosocial, and clinical risk factors in a vulnerable individual^{6–8}.

A recent and significant advance in neuropathic pain research has been the development of clinical tools, such as standardised questionnaires and quantitative sensory testing for sensory phenotyping, that differentiate and stratify neuropathic pain^{9–13}. We have entered an era whereby patients can be phenotyped in unprecedented detail in terms of sensory profile, psychological factors and physiological measures such as nerve excitability testing. We have the opportunity to combine major advances in phenotyping with genomics to improve our understanding of neuropathic pain.

Aims and objectives

DOLORisk is a multi-centre observational study that aims to understand the risk factors and determinants for neuropathic pain.

Primary objectives

The primary objectives of DOLORisk are (1) to identify the influence of demographic, environmental, psychological and clinical factors on the risk of developing and maintenance of neuropathic pain, and (2) to study the association of genetic factors with the risk of developing and maintaining neuropathic pain.

Secondary objectives

DOLORisk also aims to determine if patient stratification using physiological and psychological factors can predict neuropathic pain risk and progression. Based on the analysis of these risk factors, the study will lead to the development of a risk model for neuropathic pain, combining measurable genetic and environmental factors.

Methods

Study design

The first step was to develop a protocol that would be used by all participating centres to identify and characterise people

with neuropathic pain. The instruments chosen to phenotype DOLORisk participants were the object of a consensus meeting between the recruitment centres in October 2015. This was based on a recent international consensus on phenotyping neuropathic pain (NeuroPPIC), led by the Special Interest Group on Neuropathic Pain (NeuPSIG), of the International Association for the Study of Pain¹⁴. The respective merits and reported accuracy of available scales, questionnaires and self-reported measures were discussed and the following were included in the final DOLORisk protocol (Table 1). The DOLORisk protocol has been aligned across all recruitment centres to make data integration possible. The “core” protocol consists of questionnaires only. All participants recruited complete the core protocol and are classified according to the presence and extent of any neuropathic pain. This information will be used to look for genetic, environmental and basic clinical risk factors using the methods outlined below. The “extended” protocol consists of more detailed phenotyping and uses multiple tools. The tools used for any subject depend on the recruitment centre to which he or she is recruited (Table 2). A sub-group of participants will be recruited through the extended protocol.

Tools for phenotyping

Questionnaires

Demographics

Demographic information captured includes age, gender, weight, height, years in education, and working status.

Characterisation of pain

The presence and duration of pain (and also dysaesthesia) are assessed. Family history of chronic pain is recorded. Pain medication, analgesic relief obtained and adherence to medication are recorded according to the Brief Pain Inventory (BPI)¹⁵.

Pain intensity

Intensity of the pain is assessed with two questionnaires: the Chronic Pain Grade (CPG)¹⁶ over the past three months, and the BPI's subscale for assessment of average pain severity over 24 hours (which uses an 11 point numerical rating scale). One additional item asks about average pain over the past seven days.

Pain quality

Neuropathic descriptors of the pain are characterised with three tools: the DN4 (*Douleur Neuropathique en 4 questions*)⁹, the Neuropathic Pain Symptom Inventory (NPSI)¹⁷, and the painDETECT¹⁰. The Michigan Neuropathy Screening Instrument (MNSI)¹⁸ is used specifically for diabetic neuropathy.

Pain location

The participants are asked to indicate in which body site they feel pain. This is assessed in two ways: a list of body sites and a body map. The participants are asked to identify all the body locations in which they experienced pain over the previous three months, and to mark the pain that bothers them the most. The body sites include: Back pain; Neck or shoulder pain; Facial or dental pain; Headache; Stomach ache or abdominal pain; Pain in the arms; Pain in the hands; Chest pain; Pain in the hips; Pain in the legs or knees; Pain in the feet; Pain throughout the body (widespread pain); Other pain.

Table 1. Questionnaires of the DOLORisk protocol.

Category	Questionnaire	Core	Extended	Reference
Demographics	Age, gender, years in education, working status, weight, height	X	X	
Characterisation of pain	Presence and duration of pain	X	X	
Family history	Family history of chronic pain		X	
Pain medication	Currently taking pain medication	X	X	
	Brief Pain Inventory – Usefulness of medication		X	Cleeland and Ryan ¹⁵
	Adherence to medication		X	
Pain severity	Chronic Pain Grade	X	X	Von Korff, <i>et al.</i> ¹⁶
	Brief Pain Inventory – Pain Severity		X	Cleeland and Ryan ¹⁵
Pain quality	DN4 Questionnaire	X	X	Bouhassira, <i>et al.</i> ⁹
	DN4 Examination		X	
	Neuropathic Pain Symptom Inventory		X	Bouhassira, <i>et al.</i> ¹⁷
	PainDETECT		X	Freyenhagen, <i>et al.</i> ¹⁰
Pain location	List of locations	X	X	
	Body map		X	
Pain interference	PROMIS Pain Interference		X	Cella, <i>et al.</i> ¹⁹
Pain catastrophizing	Pain Catastrophizing Scale	X	X	Sullivan, <i>et al.</i> ²⁰
Health status and quality of life	EQ-5D-5L	X	X	Herdman, <i>et al.</i> ²¹
	PROMIS Depression	4a	8a	Cella, <i>et al.</i> ¹⁹
	PROMIS Anxiety	4a	8a	
	PROMIS Sleep Disturbance	4a	8a	
	PROMIS Fatigue		X	
	Trauma	X	X	
Disease specific (diabetic neuropathy)	Michigan Neuropathy Screening Instrument		X	Feldman, <i>et al.</i> ¹⁸
Personality	Ten Item Personality Inventory	X	X	Gosling, <i>et al.</i> ²²
	International Personality Item Pool (Emotional Stability)		X	Goldberg ²³
Lifestyle	Smoking	X	X	Campbell, <i>et al.</i> ²⁴
	Alcohol	X	X	
	International Physical Activity Questionnaire		X	Craig, <i>et al.</i> ²⁵

The core and the extended protocols take a different approach to identify the location in which the participant should be asked to rate pain. The rationale for this is that the recommendation for grading neuropathic pain is based upon pain and clinical signs in a neuroanatomically plausible distribution²⁶. The core protocol is designed for the assessment of neuropathic pain of diverse aetiologies at population level, and there is no prior expectation as to the neuroanatomically plausible distribution. Then, participants are asked to specify body regions in which they experience pain, and choose one body region in which the pain bothers them most. In the core protocol, participants are asked to answer

the questions that relates to pain intensity, quality and interference in respect to the body region in which pain bothers them most. The approach in the extended protocol is different because in these cohorts the likely aetiology of neuropathic pain is known and therefore the neuroanatomically plausible distribution is pre-determined. For instance in diabetic neuropathy or chemotherapy induced neuropathy the neuroanatomically plausible distribution is the feet, whereas following post-traumatic nerve injury the neuroanatomically plausible distribution is the innervation territory of the affected nerve. Participants are explicitly asked by the investigator to focus on the neuroanatomically plausible distribution

Table 2. Summary of tests performed during the DOLORisk protocol.

Cohort	Protocol	Neurological examination	TCSS	TNSn	Skin biopsy	QST	NCS	EEG	Threshold tracking	CPM
Population	Core									
Diabetes	Extended	X	X		X	X	X	X	X	X
Traumatic nerve injury	Extended	X	X				X		X	
Surgery	Extended	X				X			X	X
Chemotherapy	Extended	X		X		X	X		X	
Extreme phenotypes	Extended	X	X			X	X		X	

TCSS- Toronto clinical scoring system; TNSn- Total Neuropathy Score – Nurse; QST- Quantitative sensory testing; EEG - Electroencephalography; CPM- Conditioned pain modulation.

when answering the questions on pain intensity, quality and interference. To capture information on other types of pain we then ask about pain in other body regions.

Pain interference, quality of life and psychological variables

The Patient-Reported Outcomes Measurement Information System (PROMIS)¹⁹ questionnaires are used to assess various psychological and psychosocial variables. They include depression, anxiety, sleep disturbance, fatigue and pain interference. Two bespoke questions adapted from the existing population data ask about traumatic life experiences. The EQ-5D-5L²¹ measures quality of life with a visual analogue scale and five items evaluating the impact of pain on the ability of the participant to perform everyday tasks.

Two questionnaires assessing personality and in particular neuroticism are included in the DOLORisk protocol. The Ten-Item Personality Inventory (TIPI)²² evaluates extraversion, agreeableness, conscientiousness, neuroticism, and openness to experience. The 10-item International Personality Item Pool's (IPIP)²³ representation of the Goldberg²⁷ markers for Emotional Stability offers a more precise characterisation of neuroticism. Pain catastrophizing behaviours are recorded through the Pain Catastrophizing Scale (PCS)²⁰.

Lifestyle

Smoking and alcohol are recorded according to Campbell, *et al.*²⁴ The short form of the International Physical Activity Questionnaire (IPAQ)²⁵ is included in the lifestyle variables to account for physical activity.

Clinical assessment and specialised investigations

Neurological examination

A comprehensive structured upper and lower limb neurological examination is performed to detect clinical signs of a neurological lesion such as a peripheral neuropathy^{5,28–30}. The examination includes assessment of temperature (using Somedic RollTemp, Somedic AB, Sweden), light touch (using 10g monofilament) and pinprick sensation (using 'Neurotip'), joint position sense (proprioception), vibration perception using a 128Hz tuning fork, deep-tendon reflexes (using a Queen square tendon hammer and recorded as present as normal, present with reinforcement,

absent or brisk), muscle bulk, and motor power. The clinical findings for a length-dependent neuropathy are quantified with the Toronto Clinical Scoring System (TCSS)³¹. The Total Neuropathy Score – Nurse (TNSn)³² is used for chemotherapy-induced neuropathy. For other causes of neuropathic pain the spatial extent of sensory deficits and sensory hypersensitivity is recorded on a body map.

Nerve conduction studies

Nerve conduction tests, to confirm the presence of a length dependent neuropathy, are performed in line with those recommended by the American Academy of Neurology and American Association of Electrodiagnostic Medicine^{33,34}. Sural sensory and peroneal motor nerve conduction studies are performed in one lower extremity. If both studies are normal³³ no further tests are performed. If either test is abnormal additional nerve conduction studies are performed that include: ipsilateral tibial motor nerve; contralateral sural sensory nerve, peroneal motor or tibial motor nerves; or ulnar sensory, median sensory, and ulnar motor nerves in one upper extremity. The minimum case definition criterion for electrodiagnostic confirmation of a length dependant neuropathy is an abnormality of any attribute of nerve conduction studies in two separate nerves, one of which is the sural nerve. Variables such as skin temperature, age, height, gender, and weight are measured and accounted for when interpreting nerve conduction tests. Nerve conduction tests are not repeated if study participants have previous results.

Electroencephalography

Electroencephalography (EEG) reflects the summated activity of synchronised arrays of brain neurons. Establishing EEG as an appropriate biomarker for pain perception relies on its accuracy to correctly classify subjects as belonging to the pain or no-pain conditions. In order to achieve this goal we follow the standard statistical steps of multivariate pattern analysis. A range of classifiers that distinguish the painful from the non-painful brain include measures of peak activity within the various EEG frequency bands per electrode, point to point connectivity between each of 64 electrodes, as well as identification of brain networks. This is expected to allow new understanding about the neurophysiological aspects of pain processing in the painful

brain. The classification method finally employed will be the one with the highest classification accuracy on a test set after being trained on a separate training set.

Threshold tracking

Threshold tracking is an electrophysiological tool that assesses nerve excitability³⁵. Nerve excitability measures are determined by the biophysical properties of myelinated axons and the axon membrane potential. The information obtained about nerve properties is complementary to conventional nerve conduction studies³⁵. In DOLORisk several measures of axonal excitability, such as refractoriness, supernormality, strength-duration time constant and threshold electrotonus, are assessed. The excitability measures are recorded from the motor and sensory divisions of the median nerve in line with published recommendations³⁶. Training will be provided to clinicians performing threshold tracking measurements to ensure the reliability of the data and harmonisation of nerve excitability protocols in all centres.

Conditioned pain modulation

Conditioned pain modulation (CPM) provides insight into an individual's endogenous analgesic mechanisms^{37,38}. It can be assessed in a non-invasive manner and may be a key vulnerability factor for chronic pain and has also been shown to be predictive of treatment response. The protocol for CPM testing is in keeping with published recommendations^{39,40}.

Skin biopsy for intra-epidermal nerve fibre assessment

Intra-epidermal nerve fibre density (IENFD) is a validated tool for the assessment of small fibre pathology⁴¹. In DOLORisk IENFD is determined from skin biopsy samples taken in accordance with published guidelines provided by the European Federation of Neurological Societies/Peripheral Nerve Society Guideline on the utilisation of skin biopsy samples in the diagnosis of peripheral neuropathies⁴¹. The skin biopsies are taken at the end of the clinical assessment once all relevant investigations are completed. Participants do not undergo a skin biopsy if they are on warfarin or found to have other contraindications.

Quantitative sensory testing

Quantitative sensory testing (QST) is a measure of sensory perception in response to a defined sensory stimulus. This test can show abnormalities in sensory function and be used to generate a sensory profile in respect to different sensory modalities assessing both gain and loss of function. For bilateral neuropathic pain disorders such as peripheral neuropathy QST is performed unilaterally on the dorsum of the most affected foot. For unilateral neuropathic pain disorders QST is performed bilaterally in the affected area and the contralateral equivalent body region (which acts as a helpful comparator). QST is performed according to a modification of the previously published protocol of the German Research Network on Neuropathic Pain (DFNS)⁴². These modifications were made in order to improve efficiency when performed in a restricted timescale. The wind up ratio (WUR) is not performed unless the patient is having CPM in which case it will be helpful to have a measure of central sensitisation. WUR is performed on the forearm instead of the dorsum of the hand

in order to minimise the influence of peripheral sensory loss on detection of central processes. Thermal sensory limen is performed in those patients with peripheral neuropathy but not in peripheral nerve injury (a situation where it is less informative). The assessment of mechanical pain sensitivity is shortened and two rounds of tests are performed instead of the five rounds included in the full DFNS protocol. All other tests are identical to the DFNS protocol and all study sites will be trained and certificated in the DFNS protocol to promote standardisation. QST data is entered into the data analysis system, *Equista* (version 1.2.2., CASQUAR GmbH), which was developed by the DFNS. *Equista* transforms the raw QST data into z-scores thus normalising for age, gender, and the body location of testing^{43,44}. A z-score of zero is equal to the mean of the population. A score of greater or less than two standard deviations from the mean indicates gain of function or loss of function, respectively.

Genetics

DNA is extracted from a whole blood sample collected at recruitment. The analysis will follow three complementary approaches: genome-wide association studies (GWAS); whole exome sequencing to identify rare, high-impact coding variants; and targeted sequencing of selected candidate genes.

Definition of neuropathy

The participants who undergo the extended protocol are assessed for neuropathy (when this is considered a relevant possibility by the investigator e.g. a patient with diabetes) and in all cases are also graded for neuropathic pain. To diagnose peripheral neuropathy, we use the criteria outlined by Tesfaye, *et al.*⁴⁵ that classify neuropathy as possible, probable or confirmed:

Possible peripheral neuropathy is defined as the presence either of sensory symptoms, i.e. decreased sensation (e.g. "asleep, numbness"), positive neuropathic sensory symptoms (e.g. pricking or stabbing, burning or aching pain) predominantly in the toes, feet, or legs; or of sensory signs, i.e. symmetric decrease of distal sensation or unequivocally decreased or absent ankle reflexes.

Probable peripheral neuropathy corresponds to any two or more of the following: sensory symptoms (as above), decreased distal sensation, or unequivocally decreased or absent ankle reflexes.

Confirmed peripheral neuropathy is defined as the presence of an abnormality of nerve conduction studies and a sensory symptoms OR signs of neuropathy. If nerve conduction studies are normal, a validated measure of small fibre neuropathy (abnormal thermal thresholds on QST or reduced intra-epidermal nerve fibre density) may be used⁴⁵.

Definition of neuropathic pain

The Neuropathic Pain Special Interest Group (NeuPSIG) of the International Association for the Study of Pain (IASP)'s grading for neuropathic pain⁴⁶ is used to grade neuropathic pain for all study participants recruited. Each study participant's pain is assessed using these published criteria as below. Possible neuropathic pain must fulfil criteria 1 and 2. Probable neuropathic pain must

fulfil criteria 1, 2 and 3. Definite neuropathic pain must fulfil all 4 criteria.

1. Pain with a distinct neuroanatomically plausible distribution, e.g. pain symmetrically distributed in the extremities – completion of body map and clinical history.
2. A history suggestive of a relevant lesion or disease affecting the peripheral or central somatosensory system – e.g. diagnosis of diabetes mellitus and a history of neuropathy symptoms including decreased sensation, positive sensory symptoms, e.g. burning, aching pain mainly in the toes, feet or legs.
3. Demonstration of distinct neuroanatomically plausible distribution of neuropathic pain – e.g. presence of clinical signs of peripheral neuropathy, i.e. decreased distal sensation or decreased/absent ankle reflexes.
4. Demonstration of the relevant lesion or disease by at least one confirmatory test – e.g. abnormality on either the nerve conduction tests or IENFD.

In the large, population-based cohorts, the core protocol permits the ‘entry level’ approximation to a classification of “possible neuropathic pain”, based on the NeuroPPIC phenotyping consensus¹⁴. This includes positive responses to the DN4 screening questionnaire, and relevant site and severity of pain as outlined above. Additional information on diagnosis of any pain conditions will be available.

Cohorts

DOLORisk is a multi-centre cross-sectional and longitudinal observational study. Multiple cohorts with neuropathic pain from different causes will be included. Each cohort has its own specific inclusion and exclusion criteria, and follows a specific recruitment flow (Figure 1; Table 3–Table 5).

Population cohort

Generation Scotland: the Scottish Family Health Study (GS:SFHS)⁴⁷ and Genetics of Diabetes Audit and Research Tayside (GoDARTS)⁴⁸ are population-based genetic epidemiology studies. DNA, socio-demographic and clinical data are available for 24,000 GS:SFHS participants and 20,000 (9,000 with diabetes) GoDARTS participants across Scotland. Participants will be contacted by post and invited to complete the DOLORisk core protocol. After 18 months, enrolled participants will be invited to complete the same questionnaire to assess development, progression or remission of any pain. For the population cohorts it is estimated that between 7% (GS:SFHS) and 25% (GoDARTS) of those with chronic pain will have neuropathic pain⁴⁹. Therefore, 1,500 participants with neuropathic pain and 3,000 controls are anticipated from GS:SFHS and 2,000 participants with neuropathic pain and 4,000 controls are anticipated from GoDARTS.

Cross-sectional cohorts assessed with the extended protocol

Patients with peripheral neuropathic pain, e.g. diabetic neuropathy, chemotherapy-induced neuropathy, and traumatic nerve injury

will be recruited by the University of Oxford, Imperial College London, Kiel University, Technion – Israel Institute of Technology, Neuroscience Technologies, and Aarhus University, from both primary and secondary care. Patients with extreme pain phenotypes, such as insensitivity to pain, will also be recruited. The study participants will be assessed as per the DOLORisk extended protocol.

Longitudinal cohorts assessed with the extended protocol

Patients undergoing mastectomy, thoracotomy or receiving chemotherapy will be recruited by INSERM (French National Institute for Health and Medical Research) and Aarhus University. The surgical cohort of study participants will be recruited among patients scheduled for lung surgery or breast cancer surgery. The study participants receiving chemotherapy will be recruited from patients diagnosed with colorectal cancer. All study participants in this cohort will undergo the extended protocol before surgery or receiving chemotherapy. Thereafter, at different times ranging from 4 to 12 months participants will be re-assessed, using the extended protocol, to determine the development of neuropathic pain (Figure 1). We expect to include 50 patients scheduled to undergo chemotherapy and 590 patients scheduled for lung or breast surgery.

Data analysis

Sample size calculation

The sample size for the protocol is largely based on the primary outcome, which is the number of participants to explore the genetic risk factors of neuropathic pain. The main comparison will be between those study participants diagnosed with neuropathic pain and those are diagnosed with no pain or pain of non-neuropathic nature. We will also be exploring physiological and psychosocial risk factors and these outcomes will require smaller sample sizes.

For example, based on the CaTS power calculator⁵⁰, we will have 80% power in an additive model with $p=10^{-8}$, prevalence of neuropathic pain in the general population of 8%, with a disease allele frequency of 0.30 (GS:SFHS) or 0.38 (GoDARTS), and therefore a genotype relative risk of 1.34. Based on the CaTS GWAS power calculator⁵⁰, with 1,500 cases and 3,000 controls (as in the GS:SFHS cohort), we will have 82.7% power to identify SNP associations with a significance level of 5×10^{-8} , assuming an additive model, a minor disease allele frequency of 0.3, a genotypic relative risk of 1.35, and a prevalence of the diabetic neuropathic pain in the general population of 10%¹.

For the extended phenotyping of painful versus painless diabetic neuropathy (estimating 1000 subjects in each group) we will have 80% power to detect an allelic odds ratio of 1.7 at genome wide significance level ($p < 5 \times 10^{-8}$). We will also be able to cross-validate between these cohorts. We have identified a further cohort of diabetic neuropathy individuals in Sweden who will be available for replication genotyping. In collaboration with the [SUMMIT consortium](#), we would also like to combine data across diverse diabetic complications in order to enhance the power to detect genetic determinants of the microvascular complications of diabetes.

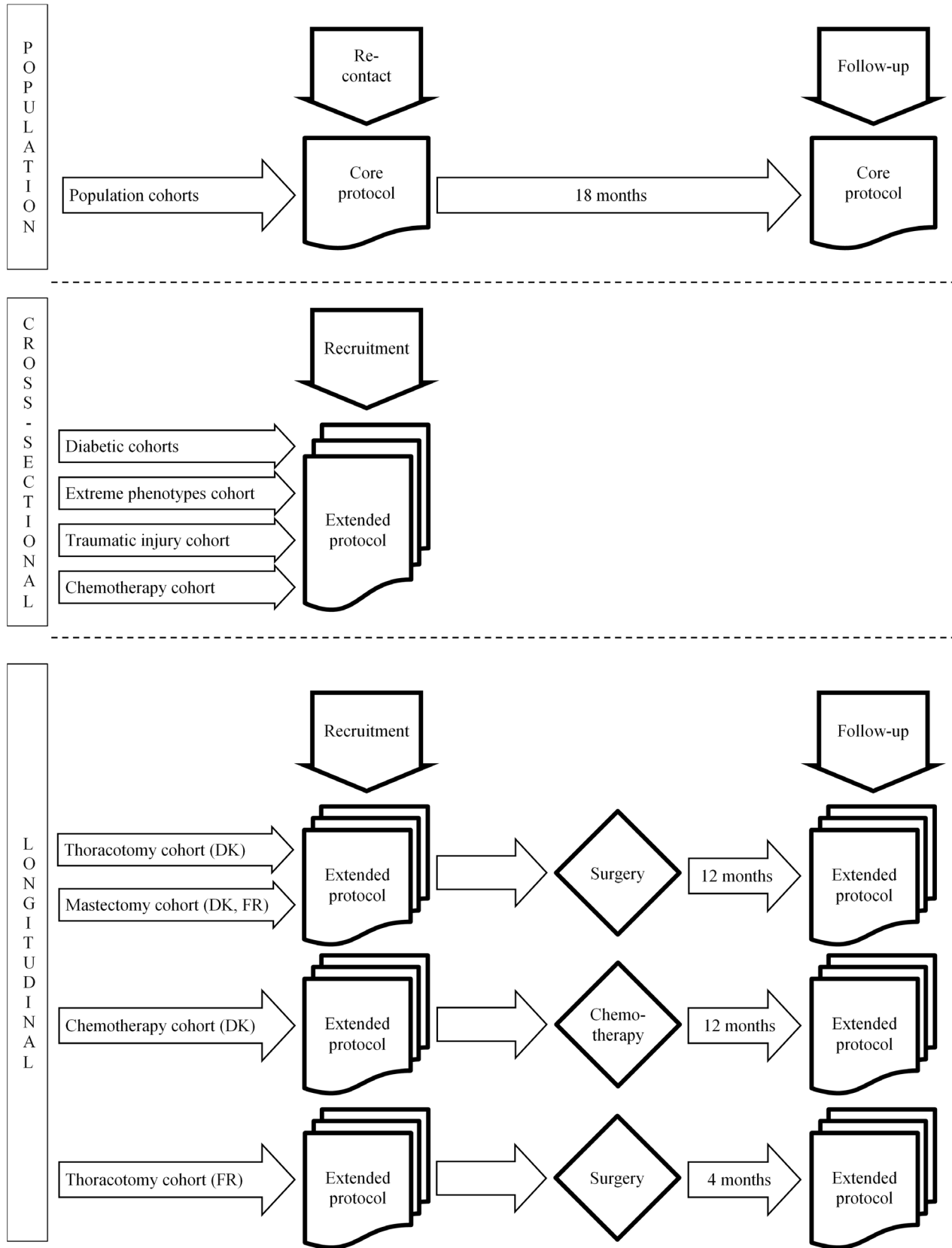


Figure 1. DOLORisk Recruitment flow. DK = Denmark, FR = France.

Table 3. Inclusion and exclusion criteria for invitation to the population cohort for the DOLORisk protocol.

	Inclusion criteria	Exclusion criteria
Population cohort	<ul style="list-style-type: none"> • Previous participation with GoDARTS or GS:SFHS. • Existing consent to be re-contacted. • Identified as being currently alive. • Currently has a postal address on file. • ≥ 18 years. 	<ul style="list-style-type: none"> • Unable to give consent. • No current postal address available. • Identified as having died.

Table 4. Inclusion and exclusion criteria for the cross-sectional cohorts for the DOLORisk protocol.

	Inclusion criteria	Exclusion criteria
Peripheral neuropathic pain	<ul style="list-style-type: none"> • ≥ 18 years with a diagnosis of peripheral neuropathy based on a prior clinical assessment combined with supportive clinical investigations such as abnormal nerve conduction studies, reduced intraepidermal nerve or abnormal findings on quantitative sensory testing. • Symptoms highly suggestive of neuropathy that in the judgement of the clinical researcher are suitable for the study even if they do not fulfil other inclusion criteria. • Patients who do not fulfil any of the exclusion criteria. • Diabetes cohorts: Type 1 or Type 2 diabetes 	<ul style="list-style-type: none"> • Pregnant. • Incapacity to give consent or to complete the study questionnaires due to insufficient language command or mental deficiencies. • Concurrent severe psychological or psychiatric disorders. • Moderate to severe pain from other causes that may confound assessment or reporting of pain (e.g. spinal canal stenosis). • Central nervous lesions, which may complicate somatosensory testing. • Patients who are in the opinion of the investigator unsuitable for participation in the study.
Extreme phenotypes	<ul style="list-style-type: none"> • ≥ 16 years with a set of symptoms that resemble those seen on Paroxysmal Extreme Pain Disorder, Familial Episodic Pain Syndrome or Erythromelalgia. • Existing diagnosis of Paroxysmal Extreme Pain Disorder or Familial Episodic Pain Syndrome or Erythromelalgia. • Reduced pain sensibility. • First degree relatives of patients who meet diagnostic criteria for Paroxysmal Extreme Pain Disorder, Familial Episodic Pain Syndrome, Erythromelalgia or inability to experience pain. • Patients who do not fulfil any of the exclusion criteria. 	<ul style="list-style-type: none"> • Pregnant. • Incapacity to give consent or to complete the study questionnaires due to insufficient language command or mental deficiencies. • Concurrent severe psychological or psychiatric disorders, especially severe claustrophobia. • Moderate to severe pain arising as a consequence of other disorders causing pain but that are not associated with those mentioned before as channelopathies. • Central nervous system diseased that may complicate the somatosensory testing. • Patients who are in the opinion of the investigator unsuitable for participation in the study. • Treatment or topical capsaicin cream/ ointment or Lidocaine patch within 30 days prior to Day 1 on the skin area that will be tested. • Presence of oedema or any skin condition at the ankle level that may interfere with the microneurography procedure.

Further sample size calculations have been performed depending on the individual outcome measures being measured.

QST

Sample size was determined according to the warm detection threshold data for patients with diabetes⁵. This calculation

revealed a minimum sample size of 34 was required per group for a power of >0.8 (difference in means 2.0; standard deviation 4.3; $\alpha = 0.05$).

CPM

A cohort of 53 subjects gives an 80% power in between group differences of >0.25 standard deviations equivalent to 1.0 to

Table 5. Inclusion and exclusion criteria for the longitudinal cohorts for the DOLORisk protocol.

	Inclusion criteria	Exclusion criteria
Chemotherapy	<ul style="list-style-type: none"> • ≥18 years. • Diagnosed with high-risk colorectal cancer. • Planned adjuvant treatment with oxaliplatin and fluorouracil (5-FU) or capecitabine (Pro 5-FU). 	<ul style="list-style-type: none"> • Known metastatic cancer. • Previous treatment with chemotherapy. • Receiving another treatment than oxaliplatin and fluorouracil (5-FU) or capecitabine (Pro 5-FU). • Significant mental illness. • Alcohol abuse. • Known diabetes. • Significant neuropathic diseases. • Spinal cord stenosis. • Peripheral vascular diseases (Fontaine >2). • Chronic pain with a pain intensity on a 0-10 numeric rating scale >5. • Patients who do not speak, read or understand Danish.
Thoracotomy	<ul style="list-style-type: none"> • ≥ 18 years. • Scheduled for lung cancer resection performed via thoracoscopy and/or thoracotomy, including lobectomy, bilobectomy, pneumonectomy, resection of the tracheobronchial bifurcation, wedge resection, sleeve resection and combinations hereof. • Willingness and ability to comply with study procedures as judged by the site investigator/manager. • Expected availability for follow-up throughout the study. 	<ul style="list-style-type: none"> • Mental incapacity or language barriers precluding adequate understanding of study procedures. • Current alcohol or substance abuse according to the site investigator's medical judgement. • Unsuitability for participation in the study for any other reason, e.g. due to a significant serious underlying condition (e.g. other cancer or AIDS), as determined by the site investigator/manager. ADDITIONALLY in FR: • Previous surgery on the same area. • Surgery targeting only the pleura or mediastinum. • Peripheral neurological pathology or central (brain damage, multiple sclerosis) susceptible to interfere with the evaluation of the post-operative pain. • History of significant mental illness: psychosis, severe depression having motivated a hospitalisation, suicide attempt. • Current major depressive episode at the time of the evaluation. • Abuse of drug or psychoactive substance during the last six months. • Patients participating in another protocol of biomedical research.
Mastectomy	<ul style="list-style-type: none"> • Women ≥ 18 years. • Scheduled for breast cancer resection performed via lumpectomy (partial or segmental mastectomy) or mastectomy with or without sentinel lymph node biopsy and axillary lymph node dissection, and any combinations hereof. • Affiliated to a social security scheme. • Danish/French language (read, written and spoken). • Willingness and ability to comply with study procedures as judged by the site investigator. • Expected availability for follow-up throughout the study. 	<ul style="list-style-type: none"> • Other cancer or AIDS. • Scheduled for bilateral mastectomy. • Presence of chronic pain before the breast cancer surgery. • Workplace accident, litigation or search for compensation. • Previous surgery on the same area. • Peripheral neurological pathology or central (brain damage, multiple sclerosis) susceptible to interfere with the evaluation of the post-operative pain. • History of significant mental illness: psychosis, severe depression having motivated a hospitalisation, suicide attempt. • Current major depressive episode at the time of assessment. • Abuse of drug or psychoactive substance during the last six months. • Cognitive or psychological disorders incompatible with the respect and/or the understanding of the protocol. • Participating in another protocol of biomedical research. • Current alcohol or substance abuse according to the site investigator's medical judgement. • Unsuitability for participation in the study for any other reason, e.g. due to a significant serious underlying condition (e.g. other cancer or AIDS), as determined by the site investigator.

1.6 range on the 0-10 pain numerical rating scale using a typical QST parameter such as conditional pain modulation.

Data management

The [University of Dundee's Health Informatics Centre \(HIC\) Services](#) acts as a hub for data management. HIC Services develops bespoke software to support secure data collection, provides recruitment support for clinical studies and manages a data entry service. All services provided by HIC are delivered within a secure Safe Haven environment to ensure data are managed safely and in compliance with Data Protection legislation. All HIC processes are governed by approved Standard Operating Procedures.

GoDARTS and GS:SFHS datasets are already hosted on secure HIC servers. Participants' identities will be shielded at all times from the research team, according to the secure SOPs.

External datasets generated by DOLORisk will be sent to HIC in anonymised format. When ready, these updated datasets will be transferred to the analytics platform held on a separate server and network from the HIC data management function within a remote-access Safe Haven for research projects. It has full analytical functionality including software (e.g. R and SAS) and is supported by powerful processing. Remote access to the Safe Haven analytics platform is available to approved project researchers, after they have signed appropriate agreements. No individual-level data can be removed from the Safe Haven, but summary outputs of analysis are released, after prompt screening by HIC to ensure that no potentially identifiable information is included to reduce the risk of accidental disclosure. Clinical phenotype data will be linked in anonymised format to genomic outputs.

Ethics and dissemination

Ethical approvals were obtained at the national level. Details can be found in [Table 6](#). Participants are included in the protocol only after having given their written informed consent. Their decision whether to take part, or withdrawal during the course of the study, in no way alters their normal medical care. The signed informed consent is obtained by the clinician in charge of the patient or the healthy volunteer.

Where possible, datasets will be made publicly available once the study is completed. Gene variants associated with neuropathic pain risk will be entered into the existing PainNetworks database⁵¹ that undergoes longstanding curation by the London Pain Consortium. Transcriptional profiling data will be entered into [painnetworks.org](#) and [ArrayExpress](#). We will enrich this with anonymised normative data on sensory profiling and physiological variables. It will be possible to download clinical screening tools from the [DOLORisk website](#).

Findings will be communicated to the scientific community via peer-reviewed publications (open access), and presentations at conferences. DOLORisk has partnered with patient organisations supporting people with pain and neuropathy-related disorders such as Pain Association Scotland, the InDependent Diabetes Trust, and Fibromyalgia Action UK. The results of the study will be sent to the organisations periodically.

Current study status

Recruitment started in 2016 and is ongoing in all centres. As of December 2017, 1,915 participants in GoDARTS and 7,240 participants in Generation Scotland have returned the questionnaires of the core protocol. 1,062 participants have been recruited throughout the rest of the centres according to the

Table 6. DOLORisk cohorts approvals. NT: Neuroscience Technologies. INSERM : Institut National de la Santé Et de la Recherche Médicale. CS: cross-sectional. Pro: prospective. REC: Research Ethics Committee. ANSM: Agence nationale de sécurité du médicament et des produits de santé (national agency for medicines and health products safety). CPP : Comité de protection des personnes (ethical research committee). CCTIRS: Comité consultatif sur le traitement de l'information en matière de recherche dans le domaine de la santé (advisory committee on data processing in health research). CNIL: Commission nationale de l'informatique et des libertés (data protection authority).

Centre	CS or Pro	Aetiology	Anticipated sample size	Ethics committee	Ethics reference	Registration link	Reference	End date
Dundee	Pro	Mixed	5500	Tayside Committee on Medical Research Ethics	05/S1401/89	https://www.hra.nhs.uk/planning-and-improving-research/application-summaries/research-summaries/dolorisk-dundee/	Smith, <i>et al.</i> ⁴⁷	April 2018
				Yorkshire & The Humber - South Yorkshire REC	15/YH/0285			
Dundee	Pro	Diabetes	3000	Tayside Committee on Medical Research Ethics	053/04	https://clinicaltrials.gov/ct2/show/NCT02783469	Hebert, <i>et al.</i> ⁴⁸	
				Yorkshire & The Humber - South Yorkshire REC	15/YH/0285			

Centre	CS or Pro	Aetiology	Anticipated sample size	Ethics committee	Ethics reference	Registration link	Reference	End date
Oxford	CS	Extreme phenotypes	100	NRES Committee London - Riverside	12/LO/0017	https://clinicaltrials.gov/ct2/show/NCT02696746		January 2019
	CS	Diabetes	300	West London REC 3	10/H0707/35	https://clinicaltrials.gov/ct2/show/NCT02672059	Themistocleous, <i>et al.</i> ⁵	June 2019
Imperial	CS	Diabetes	200	London - Bromley REC	16/LO/1470			
Kiel	CS	Mixed	200	Ethics Committee of the Faculty of Medicine of Kiel University	D454/16	https://clinicaltrials.gov/ct2/show/NCT02666456		March 2019
Technion	CS	Diabetes	200	Helsinki Committee of Rambam Health Care Campus	0052-15-RNB	https://clinicaltrials.gov/ct2/show/NCT02402361		July 2018
NT	CS	Diabetes	100	Clinical Research Ethics Committee (CREC) of idcsalud in Catalonia	2016/43-NEU-MC Mutual	https://clinicaltrials.gov/ct2/show/NCT02985294		March 2019
	CS	Traumatic	100					
Aarhus	CS	Diabetes	350	Central Denmark Region Committees on Health Research Ethics	Diabetic neuropathy, 1-10-72-130-16	https://clinicaltrials.gov/ct2/show/NCT02947828		May 2018
	CS	Chemotherapy	70	Central Denmark Region Committees on Health Research Ethics	Chronic neuropathy following chemotherapy, 20110158	https://clinicaltrials.gov/ct2/show/NCT02654691		April 2017
	Pro	Chemotherapy	50	Central Denmark Region Committees on Health Research Ethics	Acute and chronic neuropathy after oxaliplatin, 1-10-72-154-16			
Aarhus	Pro	Post-surgical	250	Central Denmark Region Committees on Health Research Ethics	Understanding risk factors and determinants for neuropathic pain after lung or breast surgery, 1-10-72-254-16 and 1-10-72-23-17	https://clinicaltrials.gov/ct2/show/NCT03124511 https://clinicaltrials.gov/ct2/show/NCT02960971		November 2019
INSERM	Pro	Post-surgical	340	ANSM	160106B-32, 160287B-32	https://clinicaltrials.gov/ct2/show/NCT02944721		November 2020
				CPP	CPP/2-16, 16 03 18			
				CCTIRS	16-331bis, 16-330bis			
				CNIL	2007306 v 0, 1251929 v 0			

extended protocol. All recruitment and follow-up activities are expected to be completed by mid-2019.

Data availability

No data are associated with this article.

Competing interests

DLB has acted as a consultant on behalf of Oxford Innovation for Abide, Biogen, GSK, Lilly, Mitsubishi Tanabe, Mundipharma and TEVA over the last 3 years. NA received speaker honoraria from Pfizer and reported fees for consultant services from Novartis, Teva, Grünenthal, Mundipharma, Sanofi Pasteur, Aptinyx. ASCR has received funding from Orion Pharma. ASCR undertakes consultancy and advisory board work for Imperial College Consultants—in the past 12 months, this has included remunerated work for: Merck, Galapagos, Toray, Quartet, Lateral, Novartis and Orion. ASCR was the owner of share options in Spinifex Pharmaceuticals from which personal benefit accrued

on the acquisition of Spinifex by Novartis in July 2015 and from which future milestone payments may occur. ASCR is named as an inventor on patents: Rice A.S.C., Vandevoorde S. and Lambert D.M Methods using N-(2-propenyl)hexadecanamide and related amides to relieve pain, WO 2005/079771 ([Google Patents](#)); Okuse K. *et al.* Methods of treating pain by inhibition of VGF activity, EP13702262.0/WO2013 110945 ([Google Patents](#)).

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Open Peer Review

Current Referee Status:



Version 1

Referee Report 05 November 2018

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Miroslav Backonja 

University of Washington, Seattle, WA, USA

This is a multicentre, international, prospective observational study with the goal to investigate in a systematic manner neuropathic pain due to multiple aetiologies targeting to enrol large number of patients, especially those with diabetic neuropathy. Authors state that the primary objective is to identify a number of factors that would influence and lead to development of neuropathic pain and the association of genetic factors with risk of developing and maintaining neuropathic pain.

This is a very ambitious and large undertaking, likely to generate a large amount of information and hopefully be a great source of publications.

A lot of thought and work has been put into this project and a few things would be worth attending to in attempt to make it more productive. These would be comments in addition to those expressed by Dr. Haroutounian with which I agree.

Statement of objectives is very general and imprecise, such as inclusion of environmental factors and none is ever addressed in the grant. It is not clear if this is matter of language used or lack of focus but for the reader of this project more precise definition of Objectives would be more meaningful.

Regarding the location of pain, the current description is detailed but probably not meaningfully useful and it is unlikely to lead to interpretable results. Yes, it will be possible to check of boxes as to location of pain but the current schemata will not provide any useful information.

Foundation for conducting studies with EEG and threshold tracking is lacking and though rationale is presented it is scientifically insufficient at best and very weak.

Is the rationale for, and objectives of, the study clearly described?

Partly

Is the study design appropriate for the research question?

Yes

Are sufficient details of the methods provided to allow replication by others?

Partly

Are the datasets clearly presented in a useable and accessible format?

Yes

Competing Interests: No competing interests were disclosed.**Referee Expertise:** Neuropathic pain assessment, QST, phenotyping, clinical trials**I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.**

Author Response 28 Jan 2019

Mathilde Pascal, Nuffield Department of Clinical Neurosciences, University of Oxford, UK

Thank you for your feedback. We have amended the article based on Dr Haroutounian's comments, which you said you agreed with – please see our response to him in addition to our reply to you below.

1. Statement of objectives is very general and imprecise, such as inclusion of environmental factors and none is ever addressed in the grant. It is not clear if this is matter of language used or lack of focus but for the reader of this project more precise definition of Objectives would be more meaningful.

Thank you for this point. We intended “environmental” to mean “non-genetic”. We agree that in this sense, it is indeed not used correctly when used for the first time in the description of the objectives. We believe the other uses are appropriate. We apologise for the confusion of the first use of the word, which we have now deleted.

2. Regarding the location of pain, the current description is detailed but probably not meaningfully useful and it is unlikely to lead to interpretable results. Yes, it will be possible to check of boxes as to location of pain but the current schemata will not provide any useful information.

The core protocol has a list of locations but the extended protocol uses this list and additionally a body map for the patient to complete, which will provide detailed information. The list of locations is a pragmatic approach in large questionnaire based surveys and was used to allow harmonisation with Generation Scotland and other ongoing epidemiological studies. This approach is consistent with the recommendations of the Neuropathic pain phenotyping by consensus recommendations of NeuPSIG (van Hecke et al, 2015). As part of our analysis, we are testing this approach to phenotype neuropathic pain, and intend to publish an analysis of the validity and feasibility of the approach. We have the advantage that in the extended cohort we can directly assess the outcome of using a list of locations versus the use of a body map. We will revise any future phenotyping efforts accordingly.

3. Foundation for conducting studies with EEG and threshold tracking is lacking and though rationale is presented it is scientifically insufficient at best and very weak.

We have now expanded on both these points in the protocol in order to provide a clearer rationale for these investigations

Competing Interests: No competing interests were disclosed.

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Pascal and colleagues present a protocol for a multicenter observational study (DOLORisk) for understanding risk factors and determinants of neuropathic pain of various etiologies. The authors should be congratulated for this massive and ambitious undertaking - the study is likely to provide enormous insight into risk factors associated with the development of neuropathic pain.

Below are several comments authors may want to consider:

The first point is related to my response related to "partial" presentation of succininet details of methods in order to be replicated.

Some of the multiple assessment in the protocol, even when following guidelines, can have certain methodological variability.

Procedures such as CPM and skin biopsy refer to general guidelines, and may be challenging to reproduce without more detailed instructions. It would be advisable if the authors added an appendix with a summary of the specific CPM protocol, and skin biopsy protocol.

Additional comments:

"Characterization of pain" section: It is unclear whether the medications will be recorded as individual drugs, as therapeutic groups vs pharmacological classes, and whether doses/duration will be recorded. It would be useful if the researchers provide the details in the protocol, and to describe how they intend to present these data.

In "nerve conduction studies" section the last sentence notes that if prior nerve conduction tests are available, repeat tests will not be performed. Do authors intend to assign an acceptable window to the timeline? i.e. - if a patient has had DPN for 10 years, and has NCV results from 8 years ago, would those considered valid for the study purposes?

Data management: it is not clear if there is a computer-based data collection system with direct data entry from each site, which then undergoes QC, or whether the data are collected on paper-pencil CRFs, then entered to a some electronic format (e.g. spreadsheets) and transmitted (via email?) to the University of Dundee HIC Services. This is important for controlling the steps where potential errors can occur, and it would be useful to provide more specific steps of data collection, entry and central storage.

Table 5: the exclusion criteria for thoracotomy and mastectomy cohorts are quite different in terms of components not related directly to the surgery (e.g. cognitive disorders, substance use). Is there a rationale for these differences?

Table 5: the sentence "Receiving another treatment than oxaliplatin and fluorouracil (5-FU) or capecitabine (Pro 5-FU)." might be better worded as "receiving treatment other than oxaliplatin...". In addition, the adjuvant FOLFOX regimen often includes Leucovorin. For such "hard" criteria of excluding anything besides 5-FU/Capecitabine and oxaliplatin, the investigators may want to add leucovorin. Also - some centers add bevacizumab to adjuvant FOLFOX regimens - consider either allowing or explicitly excluding these patients.

Is the rationale for, and objectives of, the study clearly described?

Yes

Is the study design appropriate for the research question?

Yes

Are sufficient details of the methods provided to allow replication by others?

Partly

Are the datasets clearly presented in a useable and accessible format?

Not applicable

Competing Interests: With several of the co-authors, I have collaborated on research projects, mostly as a part of various task forces and committees of IASP and its neuropathic pain special interest group (NeuPSIG). I believe these collaborations have not biased my review of the submitted manuscript.

Referee Expertise: Neuropathic pain clinical studies, QST, somatosensory phenotypic

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 28 Jan 2019

Mathilde Pascal, Nuffield Department of Clinical Neurosciences, University of Oxford, UK

Thank you for taking the time to read our study protocol and for your constructive feedback. We have addressed your comments below.

1. The first point is related to my response related to "partial" presentation of sufficient details of methods in order to be replicated. Some of the multiple assessment in the protocol, even when following guidelines, can have certain methodological variability. Procedures such as CPM and skin biopsy refer to general guidelines, and may be challenging to reproduce without more detailed instructions. It would be advisable if the authors added an appendix with a summary of the specific CPM protocol, and skin biopsy protocol.

The harmonisation of the protocols across our centres is absolutely essential in DOLORisk and we appreciate your feedback to make this protocol more useful and reproducible to other people. We have added the CPM protocol and the skin biopsy protocol in the appendices of the article. The CPM protocol also exists in video format: <https://www.youtube.com/watch?v=jL9GgdsyHtA>.

2. "Characterization of pain" section: It is unclear whether the medications will be recorded as individual drugs, as therapeutic groups vs pharmacological classes, and whether doses/duration will be recorded. It would be useful if the researchers provide the details in the protocol, and to describe how they intend to present these data.

Yes we are recording individual drugs. Wherever possible the dosage is also indicated. This section has been amended to further clarify this point.

3. In "nerve conduction studies" section the last sentence notes that if prior nerve conduction tests are available, repeat tests will not be performed. Do authors intend to assign an acceptable window to the timeline? i.e. - if a patient has had DPN for 10 years, and has NCV results from 8 years ago, would those considered valid for the study purposes?

Indeed, we take into account the results of previous nerve conduction studies if they are less than two years old, regardless of how long a participant has had DPN for. We have now added this clarification to the article.

4. Data management: it is not clear if there is a computer-based data collection system with direct data entry from each site, which then undergoes QC, or whether the data are collected on paper-pencil CRFs, then entered to a some electronic format (e.g. spreadsheets) and transmitted (via email?) to the University of Dundee HIC Services. This is important for controlling the steps where potential errors can occur, and it would be useful to provide more specific steps of data collection, entry and central storage.

The questionnaire data are collected during the visit either on a paper clinical report form, or on a digital one, depending on the participating centre. The data are then entered manually by the investigator in the DOLORisk database through a bespoke interface. In order to limit input errors, the interface includes data checks and acceptable ranges, for instance for age, height and weight. Oxford have access to the whole dataset and perform checks on the quality and completeness of the entered data. Issues such as missing data are sent back to the respective centres so that they can be addressed. The section on data management has been amended to include this information.

5. Table 5: the exclusion criteria for thoracotomy and mastectomy cohorts are quite different in terms of components not related directly to the surgery (e.g. cognitive disorders, substance use). Is there a rationale for these differences?

Most criteria are common between the mastectomy cohort and the thoracotomy cohort. Only point 4 (history of significant mental illness) might make a real difference between the French and the Danish cohort (some criteria are specific to procedure such as surgery targeting the pleura in thoracotomy). The reason for adding the exclusion criteria of significant mental illness is that our French centre wanted to avoid having problematic patients in terms of psychiatric morbidities. However the Danish centre is recording co-morbidities and we can exclude these cases at the analysis stage to match the French cohort if we feel that this is required for alignment.

The exclusion criterion of “cognitive or psychological disorders incompatible with the respect and/or the understanding of the protocol” in the mastectomy cohort is mirrored in the thoracotomy cohort by “mental incapacity or language barriers precluding adequate understanding of study procedures.” To clarify how the criteria match between the two cohorts, we have re-arranged the order of the exclusion criteria in the mastectomy cohort.

6. Table 5: the sentence "Receiving another treatment than oxaliplatin and fluorouracil (5-FU) or capecitabine (Pro 5-FU)." might be better worded as "receiving treatment other than oxaliplatin...". In addition, the adjuvant FOLFOX regimen often includes Leucovorin. For such "hard" criteria of excluding anything besides 5-FU/Capecitabine and oxaliplatin, the investigators may want to add leucovorin. Also - some centers add bevacizumab to adjuvant FOLFOX regimens - consider either allowing or explicitly excluding these patients.

We do allow leucovorin (although rare at the centre where the standard is oxaliplatin iv and capecitabine as tablet (XELOX)) while bevacizumab is not used as adjuvant therapy in Denmark, which is the centre recruiting the chemotherapy cohort. However, what we actually meant with the criteria was in fact “Not receiving oxaliplatin and fluorouracil (5-FU) or capecitabine (Pro 5-FU)”, but as this is already an inclusion criteria, we have now deleted this sentence.

Competing Interests: No competing interests were disclosed.