FULL/LONG TITLE OF THE STUDY

Partnership for Assessment and Investigation of Neuropathic Pain: Studies Tracking Outcomes, Risks and Mechanisms: Dundee Epidemiology study - investigating risk factors and possible causes of neuropathic pain

SHORT STUDY TITLE / ACRONYM

PAINSTORM Dundee Epidemiology

PAINSTORM Dundee Epidemiology Protocol Version 1 23-05-2022

This protocol has regard for the HRA guidance and order of content V1.2 March 2016

RESEARCH REFERENCE NUMBERS

IRAS Number:	304842
ISRCTN Number:	
SPONSORS Number:	2-015-22
FUNDERS Number:	MR/W002388/1

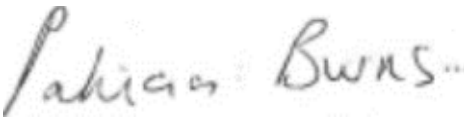
SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to GCP guidelines, the Sponsor's (and any other relevant) SOPs, and other regulatory requirements as required.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical study without the prior written consent of the Sponsor

I also confirm that I will make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies and serious breaches of GCP from the study as planned in this protocol will be explained.

For and on behalf of the Study Sponsor:

Signature: 

Date: 06/06/2022

Name (please print): **Ms Patricia Burns**

Position: Senior Clinical Research Governance Manager

Chief Investigator:

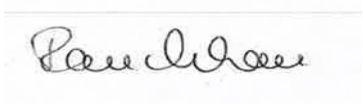
Signature: 

Date: 22/03/2022

Name: (please print): **Professor Blair H. Smith**

Position: Professor of Population Health Science

Statistician:

Signature: 

Date: 24/03/2022

Name: (please print): **Ms Petra Rauchhaus**

Position: Clinical Trials Statistician

KEY STUDY CONTACTS

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Sponsor	University of Dundee & NHS Tayside Patricia Burns, Senior Research Governance Manager Research & Development Office, TASC, Residency Block Level 3, Ninewells Hospital, Dundee, DD1 9SY 01382 383297 TASCgovernance@dundee.ac.uk
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Statistician	Petra Rauchhaus, Tayside Clinical Trials Unit, University of Dundee p.rauchhaus@dundee.ac.uk

LIST of CONTENTS

I. LIST OF ABBREVIATIONS

APDP	Advanced Pain Discovery Platform
BMI	Body Mass Index
BPI	Brief Pain Inventory
CI	Chief Investigator
CIPN	Chemotherapy-Induced Peripheral Neuropathy
CNORIS	Clinical Negligence and Other Risks Insurance Scheme
CPG	Chronic Pain Grade
GoDARTS	Genetics of Diabetes Audit and Research Tayside Study
DN4	Douleur Neuropathique En 4 Questions
DPN	Diabetic Peripheral Neuropathy
EORTC-CIPN20	European Organisation for Research and Treatment of Cancer - Chemotherapy-Induced Peripheral Neuropathy 20-item Questionnaire
EQ5D-5L	Euroquol 5 Dimensions-5 Levels
EU	European Union
FIB	Fluid Biomarker
GCP	Good Clinical Practice
GP	General Practitioner
GS:SFHS	Generation Scotland: Scottish Family Health Study
GWAS	Genome-Wide Association Study
HDL	High-Density Lipoprotein
HIC	Health Informatics Centre
HRA	Health Research Authority
IRAS	Integrate Research Application System
ISRCTN	International Standard Randomised Controlled Trials Number
LSC	Life Sciences Compute
MNSI	Michigan Neuropathy Screening Instrument
NHS	National Health Service
NRS	Numerical Rating Scale
PAINSTORM	Partnership for Assessment and Investigation of Neuropathic Pain: Studies Tracking Outcomes, Risks and Mechanisms
PCS	Pain Catastrophizing Scale

PIS	Patient Information Sheet
PROMIS	Patient-Reported Outcomes Measurement Information System
REC	Research Ethics Committee
RNA	Ribonucleic Acid
SAP	Statistical Analysis Plan
SEM	Structural Equation Modelling
SF-4a	Short Form-4 Answers
SGPALS	Saltin-Grimby Physical Activity Level Scale
SIMD	Scottish Index of Multiple Deprivation
SNP	Single Nucleotide Polymorphism
SOP	Standard Operating Procedure
STM	Senior Trial Manager
TASC	Tayside Medical Science Centre
TCTU	Tayside Clinical Trials Unit
TIPI	Ten Item Personality Inventory
TMF	Trial Master File
TMG	Trial Management Group
TRE	Trusted Research Environment

II. STUDY SUMMARY

Study Title	**PAINSTORM: Partnership for Assessment and Investigation of Neuropathic Pain: Studies Tracking Outcomes, Risks and Mechanisms. Dundee Epidemiology study.**	
PAINSTORM is a collaborative programme, led by the University of Oxford. Partners in the PAINSTORM consortium are the University of Oxford, Imperial College (London), the University of Dundee, the University of Aberdeen, and Ghent University. This protocol covers the epidemiology study being led by the University of Dundee: PAINSTORM Dundee Epidemiology study		
Study Design	Observational	
Study Participants	Cohort 1, UK: UK-Biobank Cohort 2, Scotland: SHARE (Scottish Health Research Registry) people with diabetes mellitus, people who have received potentially neurotoxic chemotherapy. Cohort 3, Scotland: GoDARTS (Genetics of Diabetes Audit and Research) people with diabetes mellitus	
Planned Sample Size	Cohort 1: 173,000 Cohort 2: 6,194 Cohort 3: 1,915	
Follow up duration	Cohort 1: 36 months Cohort 2: 18 months Cohort 3: 72 months	
Planned Study Period	5 years	
	Objectives	Outcome Measures
Primary	In people with diabetes, and/or who have received potentially neurotoxic chemotherapy, what clinical, psychosocial, demographic and genetic factors are associated with the presence of neuropathic pain at baseline and onset, worsening or remission of neuropathic pain after follow-up of up to 5 years?	MNSI/EORTC-CIPN20 questionnaires Chronic pain identification questionnaire DN4 questionnaire List of body sites
Secondary	See section 3.4	See section 3.4

III. FUNDING AND SUPPORT IN KIND

FUNDER(S)

The Advanced Pain Discovery Platform (APDP) – a 5-year initiative funded through the Government's Strategic Priorities Fund and delivered in partnership through UK Research and Innovation (Medical Research Council, Economic and Social Research Council, Biotechnology and Biological Sciences Research Council), Versus Arthritis and Eli Lilly.

IV. ROLE OF STUDY SPONSOR AND FUNDER

The roles and responsibilities of the Sponsor and Funder will be detailed in the Clinical Research Agreement and Co-Sponsor Agreement.

V. ROLES AND RESPONSIBILITIES OF STUDY MANAGEMENT COMMITEES/GROUPS & INDIVIDUALS

The Chief Investigator (CI) will be responsible for the conduct of the study. Site delegate(s) will oversee the study and will be accountable to the CI.

The study will be conducted in accordance with the principles of Good Clinical Practice (GCP).

In addition to Sponsorship approval, a favourable ethical opinion will be obtained from an appropriate NHS REC. Appropriate NHS R&D permission(s) will be obtained prior to commencement of the study.

The study will be co-ordinated by a Trial Management Group (TMG), consisting of the CI and Co-Investigators (Co-I), Study Coordinator, Senior Trial Manager (STM), Senior Research Statistician and Patient Partner(s). Other members will be added as appropriate. Minutes of the TMG will be maintained in the Trial master File (TMF).

VI. PROTOCOL CONTRIBUTORS

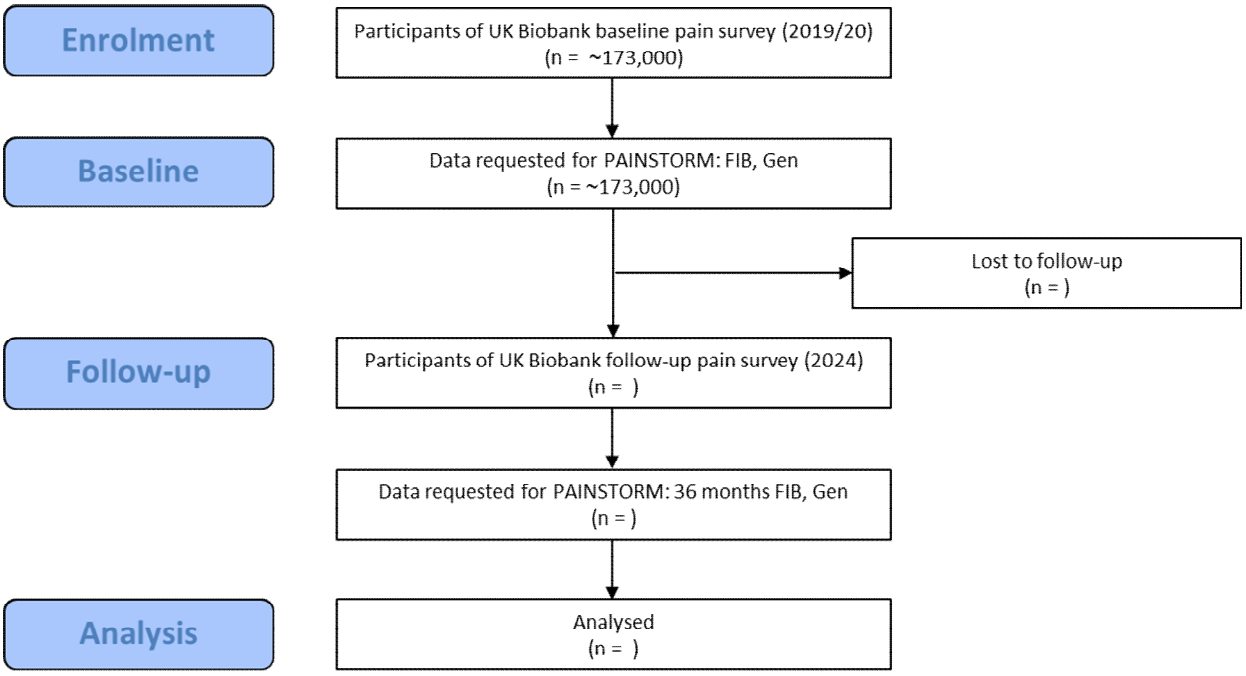
Chief Investigator, Blair H. Smith: Initial draft, review
Study Coordinator, Harry L. Hebert: Re-draft and review
Co-investigator, Lesley Colvin: Review and final approval
Co-investigator, Douglas Steele: Review
Co-investigator, Abirami Veluchamy: Review
Co-investigator, Kathryn Martin: review.
Senior Trial Manager, Margaret Band, Tayside Clinical Trials Unit, University of Dundee: Re-draft and review
Senior Research Statistician, Petra Rauchhaus, Tayside Clinical Trials Unit, University of Dundee: Review
Patient Partner, Lynn Laidlaw: Review
Patient Partner, Fiona Talkington: Review
Patient Partner, Gordon Liddle: Review
Patient Partner, Jo Josh

VII. KEY WORDS

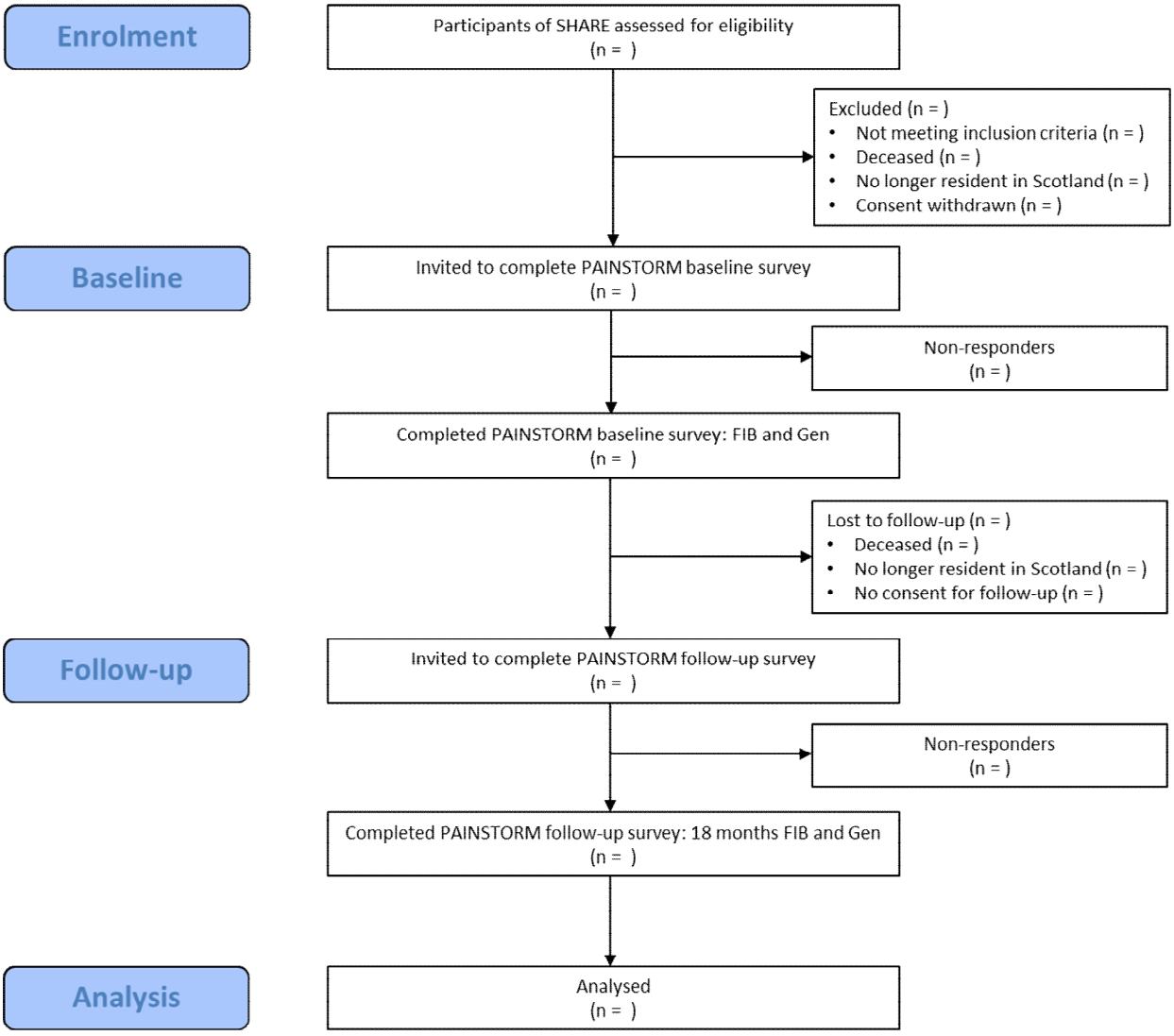
Neuropathic pain, genomics, epidemiology, neuropathy, chemotherapy induced peripheral neuropathy, diabetes.

VIII. STUDY FLOW CHART

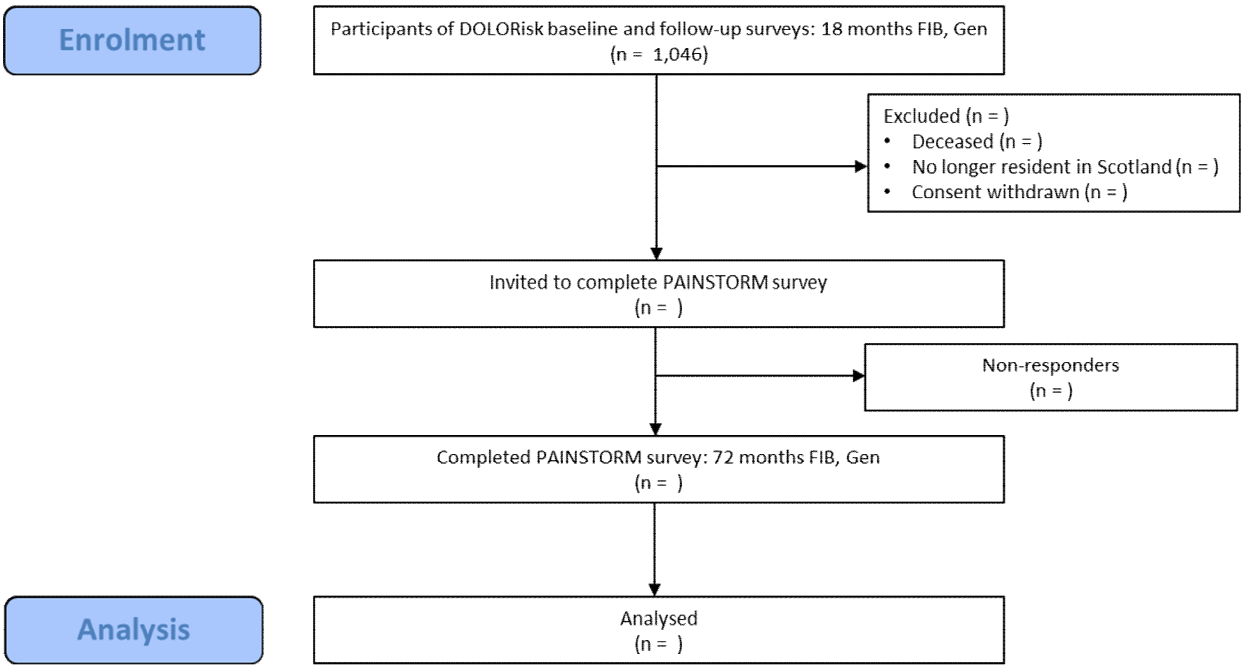
Cohort 1: UK Biobank



Cohort 2: SHARE



Cohort 3: GoDARTS



1. BACKGROUND

Neuropathic pain (NeuP) arises due to injury to the somatosensory nervous system[1]. NeuP is common affecting 7-10% of the population[2]. Crucially, not everyone with such an injury develops significant NeuP, and those who do develop it include a wide range of severity, impact, and outcomes. This variation in pain prevalence/severity involves a complex interaction between genetic, environmental and clinical factors[3]. The exact contribution and interaction of these risk/protective factors is currently unknown, but vital to understand, so that treatment and prevention can be informed. Prevalence of NeuP is projected to increase due to aging population, the diabetes/obesity epidemic and cancer survival. Unfortunately, the management of NeuP is inadequate due to poor efficacy and tolerability of current therapies[4]. First-line therapy is usually analgesic medication, although psychological strategies and neuro-modulation are applied in specialist settings. Major unmet needs for the field include: ability to predict NeuP to institute preventive strategies; understanding how best to individualise existing therapies; and improving translation from promising preclinical therapies to the clinic. Such translation requires better human cellular models, improved NeuP biomarkers and trial ready stratified cohorts[5]. The molecular, physiological and psychosocial factors underlying NeuP are too often studied in isolation and targeted as silos.

The PAINSTORM consortium is a collaboration of leading researchers in the field of NeuP/genomics/epidemiology and neuropathy, from the UK (Universities of Oxford, Dundee and Aberdeen, Imperial College London) and Belgium (University of Ghent), and Patient Insight Partners, who are people living with NeuP. Its aim is to understand NeuP pathophysiology in terms of risk factors and protective mechanisms ranging from molecular pathways to social factors, and to apply this in order to improve outcomes.

This protocol is for one component which will be led by the University of Dundee (PAINSTORM Dundee Epidemiology Study).

2. RATIONALE

This study follows on from the successful DOLORisk study,[6,7] which identified genetic and non-genetic factors associated with the presence, onset, progression and remission of NeuP, in a combination of cohort studies including population, diabetic population and specialist clinical populations. In particular, DOLORisk Dundee examined two Scottish populations (Generation Scotland: the Scottish Family Health Study [GS:SFHS][8], and the Genetics of Diabetes Audit and Research, Tayside Scotland study [GoDARTS].[9] Findings from DOLORisk Dundee have been presented at national and international conferences, and are the subject of scientific papers in advanced preparation or under review. They include identification of at least one new genetic variant found to be associated with the presence of NeuP, and clinical, psychological and socio-demographic factors found to be associated with onset, worsening or remission of NeuP over time. This was the first population-based longitudinal study of NeuP. In addition, comprehensive and systematic reviews, conducted as part of DOLORisk, identified all genetic and non-genetic factors known to be associated with the presence of NeuP.[10, 11]

These findings, though, need to be confirmed in other populations, and/or in cohorts with longer follow-up periods. PAINSTORM Dundee Epidemiology, therefore, aims to test their validity and seek other, previously unidentified associations, focusing on two conditions that confer a high risk of developing NeuP – diabetes and chemotherapy treatment. We will work with three cohorts: (1) UK Biobank, a general population cohort which has recently been re-phenotyped for pain, including NeuP; (2) members of SHARE Scotland with diabetes and/or who have received potentially neurotoxic chemotherapy; SHARE is a register of people who have volunteered to be contacted for potential research participation; and (3) members of the GoDARTS cohort who have diabetes, and who participated in the baseline and 18-month follow-up survey of DOLORisk Dundee.

2.1. Assessment and Management of Risk

In this observational study there is no risk from an intervention. The development of PAINSTORM was a partnership between clinicians, scientists and people living with NeuP. PAINSTORM Dundee Epidemiology will continue to be managed, and its outputs co-created by this grouping.

3. OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

3.1. Hypothesis

In the presence of diabetes and/or potentially neurotoxic chemotherapy, an individual's risk of developing NeuP and its outcomes can be predicted by specific psychosocial, genetic and clinical risk factors.

3.2. Aims

The ultimate aim of the PAINSTORM consortium is to reach a new understanding of NeuP, by combining molecular, physiological and psychological approaches to describe its development and progression. An inter-disciplinary approach will be used to determine the interaction of these different factors (with ‘biological’ and ‘psychosocial’ factors given equal weight) and develop innovative technologies and person-centred outcome measures to identify these pathophysiological processes in patients. The PAINSTORM Dundee Epidemiology study will contribute to this, at population level, focusing on people with diabetes and/or receiving potentially neurotoxic chemotherapy.

3.3. Primary objective

In people with diabetes, and/or who have received potentially neurotoxic chemotherapy, what clinical, psychosocial, demographic and genetic factors are associated with the presence of NeuP at baseline and onset, worsening or remission of NeuP after follow-up of up to 5 years?

3.4. Table of endpoints/outcomes

Objectives	Outcome Measures	Timepoint(s) of evaluation
Primary Objective Presence of NeuP/neuropathic descriptors		Cohort 1: 2019/20

	Chronic pain identification questionnaire DN4 questionnaire List of body sites Michigan Neuropathy Screening Instrument (Cohorts 1, 2-diabetes group and 3) European Organisation for Research and Treatment of Cancer - Chemotherapy-Induced Peripheral Neuropathy 20-item questionnaire (EORTC-CIPN20; Cohort 2-chemotherapy group)	Cohort 2: 2022 and 2023/24 Cohort 3: 2017, 2018/19, 2021/22
Secondary Objectives Severity of pain	Chronic Pain Grade (CPG) questionnaire Brief Pain Inventory (average)	Cohort 2: 2022 and 2023/24 Cohort 3: 2017, 2018/19 (CPG only), 2021/22 (CPG only)
Quality of life	EQ5D-5L questionnaire	Cohort 1: 2019/20 Cohort 2: 2022 and 2023/24 Cohort 3: 2017, 2018/19, 2021/22
Psychological health	PROMIS Depression Score PROMIS Anxiety Score PROMIS Sleep Score PROMIS Support TIPI Personality questionnaire Pain Catastrophising scale Adverse Childhood Experiences	Cohort 2: 2022 and 2023/24 Cohort 3: 2017, 2018/19 (PROMIS only), 2021/22 (PROMIS only)
Lifestyle	Smoking questionnaire Alcohol questionnaire Saltin-Grimby Physical Activity Level Scale (SGPALS)	Cohort 2: 2022 and 2023/24 Cohort 3: 2017
Demographics	Age	Cohort 1: 2019/20

	Gender Ethnicity SIMD Weight Height Years in full-time education Working status Household income	Cohort 2: 2022 and 2023/24 Cohort 3: 2021/22
Clinical	Diabetes/Chemotherapy Duration	Cohort 2: 2022 and 2023/24 Cohort 3: 2021/22
	Diabetes Type	

4. STUDY DESIGN

This is a population-based, prospective epidemiological study, focusing on identifying and replicating genetic and environmental risk factors for developing NeuP in people with diabetes and/or who have received potentially neurotoxic chemotherapy, and predicting its outcomes (remission or exacerbation). The identification of NeuP and pain-related traits and comorbidities will mainly be achieved through longitudinal survey-based questionnaires of three cohorts, UK Biobank (general population), GoDARTS (diabetes, mainly Type 2) and SHARE (general population).

5. STUDY SETTING

Cohort 1: UK Biobank, UK wide.

UK Biobank is a large-scale biomedical database and research resource, containing in-depth genetic and health information from half a million UK participants aged 40-69 years, who were registered with a GP within the NHS and recruited between 2006 and 2010.[12] The UK Biobank data relating to NeuP, including those arising from the pain re-phenotyping exercise conducted in 2019-20 and the projected follow-up in 2024 will be accessed (UK Biobank Application 49572). This will include genomic and non-genomic data, particularly relating to participants known to have diabetes.

PAINSTORM has approval to access the phenotypic and genetic data that are available for all participants (UK Biobank Application 49572; REC Reference 21/NW/0157).

Cohort 2: SHARE, Scotland wide.

SHARE is a register of people aged 11 and over, interested in participating in health research and who agree to allow SHARE to use data in their various NHS electronic records to check whether they might be suitable for health research studies.[13] The Health Informatics Centre (HIC) Dundee, a Nationally Accredited, ISO27001 certified Safe Haven, hosts SHARE and provides an environment which protects data confidentiality and ensures secure management

and processing of data. Participants in SHARE who are identified as having diabetes or who have received potentially neurotoxic chemotherapy for cancer will be invited to complete a baseline questionnaire identifying the presence or absence of NeuP and a similar follow-up questionnaire approximately 18 months later (2022 and 2023/24).

Cohort 3: Genetics of Diabetes Audit and Research Scotland cohort (GoDARTS), Tayside region.

GoDARTS is funded by the Wellcome Trust, supported by Diabetes UK and has consented patients with type 2 diabetes (over 10,000 individuals) and matching controls (over 8,000 individuals) throughout Scotland[9]. Members attend for baseline clinical, biochemical and lifestyle assessment, and have provided consent for linkage of their data to routine NHS records. They have also provided consent to be re-contacted for future research participation. A total of 1,046 GoDARTS participants (with diabetes) completed the DOLORisk study questionnaires identifying the presence or absence of NeuP at two time points, approximately 18 months apart (2017 and 2018/19), allowing assessment of the development, exacerbation or improvement of NeuP.[7] These individuals (unless lost to follow-up) will be invited to participate in one further follow-up questionnaire study as part of PAINSTORM Dundee Epidemiology.

6. PARTICIPANT ELIGIBILITY CRITERIA

6.1. Inclusion criteria

Cohort 1: UK Biobank

18 years or older

Completion of re-phenotyping exercise 2019/20

Cohorts 2 & 3: SHARE & GoDARTS

18 years or older

Existing consent to be re-contacted.

Identified as being currently alive.

Currently has a phone number, email or postal address on file

AND either:

People on the SHARE register (Cohort 2) with Diabetes Mellitus and/or who have received potentially neurotoxic chemotherapy for the treatment of cancer

Or

People on the GoDARTS register (Cohort 3) who responded to two questionnaires for the DOLORisk Dundee study (REC reference: 15/YH/0285)

6.2. Exclusion criteria

Cohorts 1, 2 & 3: Nil

7. STUDY PROCEDURES

7.1. Recruitment

7.1.1. Participant identification

Cohort 1

UK Biobank data relating to NeuP, including those arising from the pain re-phenotyping exercise conducted in 2019-20 and the projected follow-up in 2024 will be accessed via the online Access Management System. Approvals are already in place for PAINSTORM to access and analyse the UK Biobank phenotypic and genetic data that are available for all participants (REC Ref: 21/NW/0157, UK Biobank Project: 49572)

Cohorts 2

Potentially eligible people registered on SHARE will be identified by HIC. Participants contact information is held confidentially and securely by the joint GoDARTS/SHARE administration team. Prior to invitations being sent, HIC will identify people who are participants in both GoDARTS and SHARE, to ensure that those people are not included in the study twice. If someone is included in both registers, they will be invited to take part as per Cohort 3. Where someone in SHARE is identified as having both diabetes and potentially neurotoxic chemotherapy, they will be invited to participate as part of the chemotherapy group.

Potential participants will be sent an invitation by email, using templates that have already been pre-approved as part of SHARE (REC reference: 20/SS/0048). The email will include a web-based link to the Participant Information Sheet (PIS), the PAINSTORM Dundee Epidemiology questionnaire and to the PAINSTORM website. Participants will be given contact information for the research team if they wish to discuss the study before completing the questionnaire. Participants will also be given contact information to request a paper version of the questionnaire and this will be sent by post along with paper versions of the PIS, invitation letter and a pre-paid envelope.

Where an email address is not held for a participant, they will be contacted by telephone, using a pre-approved SHARE script, and invited to participate either by completing the questionnaire online or by completing a paper questionnaire. If the participant requests to complete the questionnaire online, an email will be sent to them as described above. If the participant requests a paper questionnaire, this will be sent by post along with a paper version of the PIS, an invitation letter and pre-paid envelope. Participants will be given contact information if they wish to discuss the study before completing the questionnaire.

Where both an email address and phone number are not held for a participant, they will be contacted by way of a letter sent through the post. The letter will use a template that has been pre-approved as part of SHARE. Participants will be invited to participate either by completing the questionnaire online or by completing a paper questionnaire. If the participant requests to

complete the questionnaire online, an email will be sent to them as described above. If the participant requests a paper questionnaire, this will be sent by post along with a paper version of the PIS, an invitation letter and pre-paid envelope. Participants will be given contact information if they wish to discuss the study before completing the questionnaire.

As part of the baseline questionnaire, participants will be asked whether they are interested in taking part in a follow-up questionnaire, approximately 18 months after the first. Those that respond yes will be invited by the study team (via HIC) to take part in the follow-up questionnaire, using the same contact methods as the baseline questionnaire.

Cohort 3

People on the GoDARTS register who responded to two questionnaires for the DOLORisk Dundee study (REC reference: 15/YH/0285) will be contacted. Participant contact information is held confidentially and securely by the joint GoDARTS/SHARE administration team.

Potential participants will be invited to take part by email (if an email address is held) or by telephone (if an email address is not held). The email will include web-based links to the Participant Information Sheet (PIS), the PAINSTORM Dundee Epidemiology questionnaire and to the PAINSTORM website. Participants will be given contact information if they wish to discuss the study before completing the questionnaire. Participants will also be given contact information to request a paper version of the questionnaire, and this will be sent by post along with paper versions of the PIS, cover letter and a pre-paid envelope.

Where an email address is not held for a participant, they will be contacted by telephone and invited to participate either by completing the questionnaire online or by completing a paper questionnaire. If the participant requests to complete the questionnaire online, an email will be sent to them as described above. If the participant requests a paper questionnaire, this will be sent by post along with a paper version of the PIS, an invitation letter and pre-paid envelope. The invitation letter will contain instructions on how to access the web based PIS, questionnaire and PAINSTORM website. Participants will be given contact information if they wish to discuss the study before completing the questionnaire.

Where both an email address and phone number are not held for a participant, they will be contacted by way of a letter sent through the post. The letter will use a template that has been pre-approved as part of SHARE. Participants will be invited to take part either by completing the questionnaire online or by completing a paper questionnaire. If the participant requests to complete the questionnaire online, an email will be sent to them as described above. If the participant requests a paper questionnaire, this will be sent by post along with a paper version of the PIS, an invitation letter and pre-paid envelope. Participants will be given contact information if they wish to discuss the study before completing the questionnaire.

7.2. Payment

Not applicable.

7.3. Consent

Cohort 1

Not applicable. UK-Biobank participants have given their consent for their data to be used for research. Individual participants will not be contacted about the study. Consent for the use of their data will be via the UK Biobank access team.

Cohort 2 & 3

The submission of a completed questionnaire will be taken as consent to participate in the PAINSTORM Dundee Epidemiology study. Participants will be asked for consent to be contacted about future studies. If this has not been answered on the paper questionnaire the answer will be assumed to be “no”. Participants will also be asked for consent to link the data they provide in the questionnaires to routinely collected electronic NHS medical records, held securely by HIC. If this has not been answered on the paper questionnaire the answer will be assumed to be “no”.

7.3.1. Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable

Consent will be sought to allow contact from other researchers within the PAINSTORM consortium carrying out the qualitative work package. This is a separate protocol and participants may be contacted and invited to take part. A separate PIS and consent process will be carried out for this study. Participants are free to decline to take part in qualitative study, this will not affect their participation in PAINSTORM Dundee Epidemiology study.

7.4. Study assessments

The following data will be collected from participants via the PAINSTORM Dundee Epidemiology questionnaire either on-line or in paper format depending on participants’ preferences. The main survey will be preceded by a pilot survey of 200 individuals, to test the e-mail and telephone processes and the questionnaire.

Demographics: Age, gender, ethnicity, time in full-time education, working status, household income.

Psychological factors: adverse childhood experiences, hospital stays

Lifestyle: smoking history, alcohol consumption, physical activity

Clinical factors: diabetes/chemotherapy duration, type of diabetes, height and weight

Questionnaires:

- CPG 3-month average NRS (pain intensity)
- BPI overall average (pain intensity)
- PROMIS SF-4a (depression, anxiety, sleep disturbance, support)

- TIPI (extraversion, agreeableness, conscientiousness, emotional stability, open to new experiences)
- PCS (pain related worrying)
- MNSI (diabetic neuropathy)
- EORTC-CIPN20 (CIPN)
- EQ5D-5L (health related quality of life)

Where available the following data will be collected via data linkage.

Demographics: Social deprivation

Clinical factors: Body Mass Index (BMI), resting heart rate, blood pressure, medical history of cardiovascular disease.

Biomarkers: glucose, HbA1c, creatinine, total cholesterol, high density lipoprotein (HDL)

Genetics: genome wide

Appendix 1 (Section 14.1) shows the schedule of procedures for all cohorts.

Cohort 1

Use of previously obtained data only

Cohort 2

Participants will be invited to complete the PAINSTORM Dundee Epidemiology questionnaire at baseline and at 18 months.

Cohort 3

Participants previously completed two DOLORisk questionnaires 18 months apart. These will be used for baseline and 18-month follow-up for the PAINSTORM Dundee Epidemiology study. Participants will be contacted 72 months after they completed the DOLORisk baseline questionnaire to complete the PAINSTORM Dundee Epidemiology questionnaire.

7.5. Long term follow-up assessments

No long-term follow-up is planned, however, all participants consented will be asked if they wish to be contacted about future research.

7.6. Withdrawal criteria

All participants are free to withdraw at any time and are not obliged to give reason(s). Where possible, if participant agrees, the reason for withdrawal will be recorded. If a participant withdraws or is withdrawn their data collected up to that point will be retained unless the participant expresses the wish to withdraw their data and or tissue. Those withdrawn, including those lost to follow-up, will be identified and a descriptive analysis of them provided, including the reasons for their loss, if known, and its relationship to treatment and outcome.

7.7. End of study

The end of study is defined as the last participant contact. The Sponsor and/or CI have the right at any time to terminate the study for clinical or administrative reasons.

The end of the study will be reported to the Sponsor, REC and NHS R&D Office(s) within 90 days.

A final clinical study report will be submitted to the Sponsor and REC within 1 year of the end of the study.

8. STATISTICS AND DATA ANALYSIS

At baseline and follow-up, the following important phenotypic groups will be identified in each cohort, using data from the PAINSTORM Dundee Epidemiology questionnaire: (1) those without chronic pain; (2) those with chronic non-NeuP; and (3) those with chronic NeuP. These groups will be defined using the chronic pain identification and DN4 items in the questionnaire. Sub-groups will also be identified from these three main phenotypes (see section 8.5).

By comparing these groups at baseline and follow-up, we will be able to identify those who have incident NeuP (those who have developed NeuP *de novo* since the baseline questionnaire was completed), resolved NeuP (those who previously had NeuP, but no longer have it) and persistent NeuP (those whose NeuP remains, but may have improved, become worse or remained the same in severity). The lack of previous longitudinal studies on NeuP makes it difficult to estimate the numbers in these groups. In our previous DOLORisk study with GoDARTS (people with diabetes), over 18 months the incidence of NeuP was 10.7% (paper in preparation). In the general population (GS:SFHS) study, the incidence over the same 18-month period was 6.0%. The estimated prevalence of NeuP in people receiving potentially neurotoxic chemotherapy is 30% after one year.[14]

In all cohorts, we will identify the environmental factors (age, gender, ethnicity, lifestyle, socio-demographic and co-morbidity) associated with the presence, incidence, resolution and persistence of NeuP using chi-square testing, and measure their magnitude using regression analysis. We will develop an initial model through regression-based analysis, to distinguish factors independently associated, and also quantify interactions and confounding between factors. Using the high-quality GWAS data available for UK Biobank, SHARE and GoDARTS, case-control studies will identify the genetic factors (single nucleotide polymorphisms [SNP]) associated with chronic NeuP in those with diabetes and those receiving potentially neurotoxic chemotherapy.

Using both the environmental data and the GWAS data we will seek to develop three sub-models/algorithms explaining NeuP and painful peripheral neuropathy among diabetic and chemotherapy patients in UK Biobank, SHARE and GoDARTS:

a) *Genetic model*: an additive genetic model based on regression analysis to predict the onset, persistence and/or progression of NeuP, based on significant SNPs in the genome-wide association studies.
b) *Environmental model*: a regression model to reflect environmental factors and their relationship with NeuP presence, onset, persistence and remission.
c) *Gene-environment interaction model*: a regression model with NeuP onset, persistence and/or progression as outcome, and dosage of alleles for each genetic variant as predictors,

adjusting for demographic covariates, with the specific aim of evaluating the interaction between environmental/life course exposures and genetic variants.

8.1. Planned recruitment

Cohort 1 has already provided their data (n ~173,000) in response to the UK Biobank pain re-phenotyping exercise. PAINSTORM has approval to access the phenotypic and genetic data that are available for all participants.

Cohort 2 includes approximately 18,000 individuals with diabetes, and an estimated 600 who have received potentially neurotoxic chemotherapy. We aim for a response rate of 33.3% (consistent with the baseline response rate in GoDARTS during the DOLORisk study), which will generate study samples of 5,994 and 200 respectively.

Cohort 3 includes approximately 1,000 people with diabetes who participated in baseline and follow-up surveys for DOLORisk. We aim for a response rate of 67% (consistent with the follow-up response rate in GoDARTS during the DOLORisk study), which will generate a sample of 667 participants in whom NeuP progress can be tracked over 5 years at three time points.

8.2. Sample size calculation

Cohort 1: Assuming a NeuP prevalence of 10% in the general population and 25% in the diabetic population (painful diabetic peripheral neuropathy [DPN]), we will have a sample size of 17,300 NeuP cases and 155,700 no-NeuP controls in the UK Biobank, with 2,714 having painful DPN and 8,141 without painful DPN.

Cohort 2: Assuming the same NeuP prevalence in the diabetic population and a prevalence of 30% in the chemotherapy population (painful CIPN), we will have a sample size of 1,499 painful DPN and 1,600 without painful DPN in SHARE, and 60 with painful CIPN and 140 without painful CIPN.

Cohort 3: In the first DOLORisk questionnaire (which is being used as baseline), 482 participants had NeuP and 1,094 had no-NeuP in GoDARTS, and 45 participants had painful DPN and 130 without painful DPN.

8.3. Statistical analysis plan (SAP)

The data will be analysed by three separate groups, so three different analysis plans will be developed for different parts of the data analysis:

1. The analysis of genetic data will be led by the study coordinator and aims to determine which variants (SNPs) influence the development, severity and remission of NeuP. Genetic variants will be identified using a genome-wide association study approach. Genetic analysis will be based on cohort, disease group and NeuP group and aims to identify genes that identify each group. A description of the genetics analysis will be provided in an analysis plan.
2. Machine learning and structural equation modelling (SEM) will be performed by collaborators at the University of Oxford to:

- Produce a ranking of predictive features and determine which ones are most powerful.
- Describe clinical subgroups of patients sharing the same traits and features, which will aid patient stratification.
- Exploit the large phenotypically harmonised cohorts available within PAINSTORM to develop cross-validated predictive models for the clinical subgroups of NeuP identified by the SEM.

PAINSTORM Dundee Epidemiology, will contribute to sophisticated statistical and computational approaches to modelling and quantifying associations with NeuP presence and development, testing their strength and validity. This will adopt two distinct principled approaches: (1) examining all available factors, with a view to understanding the biology of NeuP; and (2) focusing on factors and techniques with the greatest clinical utility, with a view to applying the findings in real-world medical practice. Ultimately, we will develop composite biomarkers signatures for NeuP21, enabling greater understanding of NeuP as well as individualised assessment, and therefore stratified treatment or prevention approach.

3. Questionnaires, biomarkers, lifestyle and health data will be analysed by the study coordinator. The analysis will be based on cohort, disease group and NeuP group and aims to determine factors that influence the presence, development, persistence and remission of NeuP.

8.4. Statistical analysis of clinical data

This is an exploratory study that aims to identify predictors of NeuP presence, development, persistence and remission in different disease groups. The three cohorts recruited differ in patient composition, disease group and data collection points. There is therefore no unified primary or secondary endpoint that covers all cohorts. All outcomes are exploratory.

All continuous variables will be summarised using the following descriptive statistics: n (non-missing sample size), number of missing records, mean, standard deviation, median, maximum and minimum.
The frequency and percentages (based on the non-missing sample size) of observed levels will be reported for all categorical measures.
All summary tables will be structured with a column for each disease group and NeuP group and an additional column for the total population relevant to that table/treatment, including any missing observations

8.4.1. Summary of baseline data

Baseline data for all analysis are age, sex, weight, height, BMI, SIMD, years in full-time education, working status and household income.

8.4.2. Primary outcome analysis

Not applicable, see section 8.4

8.4.3. Secondary outcome analysis

Not applicable, see section 8.4

8.5. Subgroup analyses

Subgroups will be specified separately for each cohort and detailed in the SAP. They will include:

- Patients with painful, painless and no peripheral neuropathy (defined using the chronic pain identification, DN4 and EORTC-CIPN20/MNSI screening tools)
- Patients with painful, painless and no neuropathy post chemotherapy (defined using the chronic pain identification, DN4 and EORTC-CIPN20 screening tools)
- Patients with painful, painless and no diabetic neuropathy (defined using the chronic pain, DN4 and MNSI and screening tools)
- Other subgroups as identified in the clinical and genetic analysis

8.6. Adjusted analysis

For each cohort and NeuP category, the aim is to build a predictive model of NeuP activity including the major predictive factors.

8.7. Participant population

All patients in this study are selected based on medical history data. No treatment will be applied. The patient population for analysis will be all patients included in the study.

8.8. Procedure(s) to account for missing or spurious data

Strategies for missing or spurious data will be detailed in the SAP.

9. DATA MANAGEMENT

9.1. Bioinformatics and Data management

Data management will be undertaken in close collaboration with HIC Services, which operates a secure research environment with strong data governance for the provisioning of data to academics and other users to improve healthcare and population health. All services provided by HIC are delivered within a secure environment to ensure data are managed safely and in compliance with Data Protection legislation, and all HIC processes are governed by approved SOPs. The GoDARTS and DOLORisk datasets are already hosted on secure HIC servers, in collaboration with the study investigators. Participants' identities will be shielded from the research team, according to the secure SOPs. Participants will be invited to complete the online or paper version of the PAINSTORM Dundee Epidemiology questionnaire. Paper questionnaires will be returned to HIC with the anonymised study code for identification. Where participants include any personal information this will be separated and stored confidentially, and study data will be entered into the PAINSTORM database.

Access to the database is restricted to approved researchers within the PAINSTORM study and individual accounts are protected by unique username and password. Anonymised data generated from PAINSTORM Dundee Epidemiology will be made available for the PAINSTORM study team to download for analysis on secure computers owned and maintained by the University of Dundee. At the same time, UK Biobank data relating to NeuP, including those

arising from the pain re-phenotyping exercise conducted in 2019-20 and the projected follow-up in 2024 will be downloaded via the secure online Access Management System for analysis in the same environment as the data generated from PAINSTORM Dundee Epidemiology. Access to the computers is through a personalised account, protected by unique username and password, meaning only the PAINSTORM research team will have access to the data. Analytics platforms used will include the Life Sciences Computing (LSC) cluster, maintained by the School of Life Sciences at the University of Dundee, which will be used for all analyses involving genome-wide data. The LSC cluster runs in a UNIX/LINUX environment and has full analytical capability, with the storage capacity (~250Gb) to handle large genome-wide datasets. Access to the LSC cluster is restricted to approved project researchers and data files are restricted by individual-level access permissions. The GoDARTS, UK Biobank and SHARE genetic datasets are already approved for storage on the LSC cluster for other phenotypic studies, but only the PAINSTORM research team will have access to genetic data relating to the PAINSTORM Dundee Epidemiology study.

The main survey will be preceded by a pilot survey of 200 individuals, to test the mailing process and the questionnaire. The intention will be to include the data from the pilot survey with the data from the main survey unless there are substantial revisions to be made to the questionnaire.

Data generated from PAINSTORM Dundee Epidemiology will be linked to genetic, clinical and biomarker data obtained as part of the original recruitment process for the GoDARTS study. Data generated from PAINSTORM Dundee Epidemiology will also be made available in a Trusted Research Environment (TRE; also known as a Safe Haven), maintained by HIC, to allow electronic linkage with routinely collected NHS data including biomarker and clinical variables. It has full analytical functionality including software (e.g. R) and is supported by powerful processing. Remote access to the TRE analytics platform is only available to approved project researchers, after they have signed appropriate agreements, and this provides an efficient multi-user platform for analysing shared or collaborative datasets. Data can only be analysed in the TRE, with remote access available by internet worldwide. No individual-level data can be removed from the TRE, but summary outputs of analysis (e.g. tables) are released, after prompt screening by HIC (to ensure that no potentially identifiable information is included to reduce the risk of accidental disclosure).

Individual level data generated from PAINSTORM Dundee Epidemiology will be made available to approved researchers and collaborators from outside the University of Dundee. These may be from commercial companies and may be from outside of the UK and EU. One of these collaborators is the University of Oxford, led by Professor David Bennett (PAINSTORM study co-ordinator), who will assess the data for the purposes of curation, analysis and project harmonisation, research governance, quality control and to monitor recruiting progress. Individual patient level data shared with approved collaborators will be in accordance with NHS Data Protection standards and will be anonymised through study PROCHI numbers (generated by HIC to anonymise NHS Scotland Community Health Index numbers), allowing participants'

identities to be shielded from project researchers. Access to the data will be restricted to approved researchers by username and password.

9.2. Data collection tools and source document identification

Study questionnaires will be used as source data.

The study database will be based on the protocol for the study and individual requirements of the investigators. The database is managed in line with all applicable principles of medical confidentiality and UK law on data protection. The Data Controller will be the University of Dundee and the Data Custodian will be the CI.

Development and validation of the study database, quality control and extraction of data will be done according to HIC and TASC procedures. Extracts for analysis will be managed by the CI.

9.3. Access to Data

Direct access will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit study-related, audits and inspections - in line with participant consent.

9.4. Archiving

Archiving will be authorised by the Sponsor following submission of the end of study report. All essential documents will be archived for a minimum of 5 years after end of study, destruction of essential documents will require authorisation from the Sponsor.

10. AUDIT & INSPECTION

The CI, Co-Is and all institutions involved in the study will permit study related monitoring, audits, and REC review. In the event of an audit, the CI will allow the Sponsor, representatives of the Sponsor or regulatory authorities direct access to all study records and source documentation.

11. ETHICAL AND REGULATORY CONSIDERATIONS

11.1. Research Ethics Committee (REC) review & reports

Before the start of the study, approval will be sought from a REC for the study protocol, and other relevant documents. Substantial amendments that require review by REC will not be implemented until the REC grants a favourable opinion for the study.

All correspondence with the REC will be retained in the Trial Master File. A copy of all REC reports will be submitted to the Sponsor.

An annual progress report will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the study is declared ended. It is the Chief Investigator’s responsibility to produce the annual reports as required.

The Chief Investigator will notify the REC of the end of the study. If the study is ended prematurely, the Chief Investigator will notify the REC, including the reasons for the premature termination

Within 1 year after the end of the study, the Chief Investigator will submit a final report with the results, including any publications/abstracts, to the REC

11.2. Peer review

Extensively reviewed by the funders as part of the award process, UK Research and Innovation (Medical Research Council), Versus Arthritis and Eli Lilly, via their Advanced Pain Discovery Platform.

11.3. Public and Patient Involvement

The PAINSTORM proposal was developed by a team of patients, clinicians and researchers, inspired by research and conversations with people living with NeuP. Patient partners have actively shaped content to ensure unmet needs have been addressed. Discussions with people living with NeuP were held to uncover relevant research priorities for PAINSTORM, centred on individuals' experience of pain and the best way to assess pain.

Three individuals have volunteered to be patient partners for PAINSTORM Dundee Epidemiology on the main research team (named in the protocol contributors section). The protocol has been reviewed by these patient partners. A patient partner will attend research ethics committee meetings so that they can describe what is being done with patients in patient/public facing materials (e.g., information leaflets). All information material, such as participant information sheets and lay summaries, have been written in plain English and reviewed by the patient partners to ensure people can find out what they want to know in an understandable way. The patient partners will be invited to become a member of the Trial Management Group and attend meetings to give their input into how the study is being carried out. Patient partners will be involved in analysis and interpretation of findings to ensure that emerging knowledge makes sense to those with lived experience.

11.4. Regulatory Compliance

The study will not commence until favourable REC opinion is obtained. Before the site can enrol participants into the study, the CI/Co-Is or designee will ensure that appropriate approvals (NHS R&D) from the participating organisation is in place.

For any amendment to the study, the CI or designee, in agreement with the sponsor, will submit information to the appropriate body in order for them to issue approval for the amendment. The CI or designee will work with the site (R&D department at NHS site as well as the study delivery team) so they can put the necessary arrangements in place to implement the amendment to confirm their support for the study as amended.

11.5. Protocol compliance

Prospective, planned deviations or waivers to the protocol are not allowed and must not be used e.g. it is not acceptable to enrol a participant if they do not meet the eligibility criteria or restrictions specified in the study protocol. Accidental protocol breaches can happen at any

time. They must be adequately documented on the relevant forms and reported to the CI and Sponsor immediately.

Breaches from the protocol which are found to frequently recur are not acceptable, will require immediate action and could potentially be classified as a serious breach.

In the event that there is a breach of the protocol, the nature of and reasons for the breach will be recorded in the TMF and documented in the study TASC Breach Log and reported to Sponsor via the breach reporting process.

As the questionnaires are self-complete, where participants do not complete all questions of the PAINSTORM Dundee Epidemiology questionnaire or do not complete the follow up questionnaires, these will not be recorded as breaches. Where there is data which is not available for some participants this will not be recorded as a breach. Procedures to account for missing data will be detailed in the SAP.

11.6. Notification of Serious Breaches to GCP and/or the protocol

A “serious breach” is a breach which is likely to effect to a significant degree –

a) the safety or physical or mental integrity of the participants of the study; or
b) the scientific value of the study

The sponsor will be notified immediately of any case where the above definition applies during the study conduct phase

The sponsor will liaise with REC about any serious breach of

a) the conditions and principles of GCP in connection with the study; or
b) the protocol relating to that study.

11.7. Data protection and patient confidentiality

The CI and study staff will comply with the requirements of the EU Data Protection Directive (Directive 95/46/EC) or any subsequent amendment or replacement thereof with regard to the collection, storage, processing and disclosure of personal information and will uphold the Directive’s core principles.

The CI and study staff will also adhere to the NHS Scotland Code of Practice on Protecting Participant Confidentiality or equivalent.

All study records and data will be managed in a manner designed to maintain participant confidentiality. All records, electronic or paper, will be kept in a secure storage area with access limited to appropriate study staff only. Computers used to collate data will have limited access measures via usernames and passwords.

Personal clinical information will not be released without the written permission of the participant, except as necessary for monitoring or auditing by the Sponsor, its designee or regulatory authorities.

The CI and study staff will not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished, confidential information disclosed to those

individuals for the purpose of the study. Prior written agreement from the Sponsor will be required for the disclosure of any said confidential information to other parties.

Access to collated participant data will be restricted to the CI and appropriate delegated study staff. Where data requires to be transferred, an appropriate Data Transfer Agreement will be put in place.

Published results will not contain any personal data that could allow identification of individual participants.

11.8. Financial and other competing interests for the Chief Investigator, Co-Is at each site and committee members for the overall study management

The study team declare no relevant competing interests.

11.9. Indemnity

The University of Dundee and Tayside Health Board are Co-Sponsoring the study.

Insurance. – The University of Dundee will obtain and hold Professional Negligence Clinical Trials Insurance cover for legal liabilities arising from the study.

Tayside Health Board will maintain its membership of the Clinical Negligence and Other Risks Insurance Scheme (CNORIS) which covers the legal liability of Tayside in relation to the study.

Where the study involves University of Dundee staff undertaking clinical research on NHS participants, such staff will hold honorary contracts with Tayside Health Board which means they will have cover under Tayside's membership of the CNORIS scheme.

Indemnity. The Co-Sponsors do not provide study participants with indemnity in relation to participation in the study but have insurance for legal liability as described above.

11.10. Amendments

The CI will seek Sponsor approval for any amendments to the Protocol or other approved study documents. Amendments to the protocol or other study documents will not be implemented without approval from the Sponsor and subsequent approval from the appropriate REC, as appropriate, and NHS R&D Office(s).

11.11. Post study care

Not applicable

11.12. Access to the final study dataset

The CI and Study Statistician will have access to the final study dataset. Access to the final study dataset to others will be approved by the CI.

12. DISSEMINATION POLICY

12.1. Dissemination policy

There will be a clear PAINSTORM strategy for reporting and dissemination of scientific output, overseen by a dissemination committee. Patient partners will be invited to be part of the dissemination committee. Patient partners will lead the identification of ways of disseminating

the results and review outputs aimed at patients and public. Results will be written up in high impact open access scientific papers and presented at scientific conferences internationally. The criteria for authorship will follow the criteria of The International Committee of Medical Journal Editors. A PAINSTORM website will be created, with public access, and papers will be shared there. Where results potentially affect patient care, e.g. through the identification of stratified approaches to risk management, these will be shared with stakeholders such as patient groups, national regulatory and professional bodies, health professionals and the general public, with a view of maximising overall impact. A Final Report will be prepared for the funding body and for the Ethics Committee.

12.2. Authorship eligibility guidelines and any intended use of professional writers

The data arising from this study resides with the study team and ownership with the University of Dundee. On completion of the study, the study data will be analysed and tabulated, and a clinical study final report will be prepared. The criteria for authorship will follow the criteria of The International Committee of Medical Journal Editors. The CI will be responsible for authorship of the final report.

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14. APPENDICIES

14.1. Appendix 1 – Schedule of Procedures

Cohort 1 UK-Biobank		
	Baseline	Month 36
FIB: Fluid bio-marker data (i.e. serum, RNA)	X	X
Gen: Genomics data	X	X

FIB & Gen data previously collected by UK biobank and accessed for PAINSTORM Dundee Epidemiology

Cohort 2: SHARE		
	Baseline	Month 18
PAINSTORM Dundee questionnaire	X	X
FIB: Fluid bio-marker data (i.e. serum, RNA)	X	X
Gen: Genomics data	X	X

FIB & Gen data previously collected by SHARE and accessed for PAINSTORM Dundee Epidemiology

Cohort 3: GoDARTS			
	Baseline	Month 18	Month 72
DOLORisk questionnaire data	X	X	
PAINSTORM Dundee questionnaire			X
FIB: Fluid bio-marker data (i.e. serum, RNA)	X	X	X
Gen: Genomics data	X	X	X

FIB & Gen data previously collected by GoDARTS and accessed for PAINSTORM Dundee Epidemiology
Baseline and Month 18: historical data. Month 72: to be scheduled from date of DOLORisk Dundee baseline.

14.2. Appendix 2 – Amendment History

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made