PAINSTORM FULL/LONG TITLE OF THE STUDY

PAINSTORM: Partnership for Assessment and Investigation of NeuP: Studies Tracking Outcomes, Risks and Mechanisms

SHORT STUDY TITLE / ACRONYM

PAINSTORM Dundee CIPN study

PAINSTORM Dundee CIPN Protocol V1.0 25-05-22

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

RESEARCH REFERENCE NUMBERS

IRAS Number: 303039 SPONSORS Number: 2-016-22

ISRCTN Number: FUNDERS Number:

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator (CI) agrees to conduct the study in compliance with the approved protocol and will adhere to Good Clinical Practice (GCP) guidelines, the Sponsor's (and any other relevant) Standard Operating Procedures (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:
.....

Name (please print):

.....

Position:

.....

Chief Investigator:

Signature: .....  ..... Date: 10/06/.2022

Name: (please print):

.....Lesley A Colvin.....

Statistician:

Signature:

.....

Name: (please print):

.....

Position:

.....

KEY STUDY CONTACTS

Chief Investigator	Lesley A Colvin, Prof of Pain Medicine, Division of Population Health and Genomics, University of Dundee, Mackenzie Building, Ninewells Hospital, Dundee, DD1 9SY l.a.colvin@dundee.ac.uk
Study Coordinator/ Clinical Felllow	Dr Clare Clarke Division of Population Health and Genomics, University of Dundee, Mackenzie Building, Ninewells Hospital, Dundee, DD1 9SY c.z.clarke@dundee.ac.uk
Sponsor	University of Dundee Patricia Burns, Senior Research Governance Manager Research & Development Office, TASC, Residency Block Level 3, Ninewells Hospital, Dundee, DD1 9SY TASCgovernance@dundee.ac.uk
Funder(s)	UK Research and Innovation Versus Arthritis Elli Lilly
Clinical Trials Unit	Tayside Clinical Trials Unit (TCTU), Margaret Band, Senior Trial Manager m.band@dundee.ac.uk TASC, Residency Block, Level 3, Ninewells Hospital, Dundee, DD1 9SY TCTU@dundee.ac.uk
Key Protocol Contributors	Blair Smith, Professor of Population Health Science, Division of Population Health and Genomics, University of Dundee b.h.smith@dundee.ac.uk Margaret Band, Senior Trial Manager, TCTU, University of Dundee, m.band@dundee.ac.uk Douglas Steele, Professor of Neuroimaging, University of Dundee d.steele@dundee.ac.uk Dr Abirami Veluchamy, Postdoctoral Researcher, Division of Population Health and Geonomics, University of Dundee a.z.veluchamy@dundee.ac.uk Dr Kathryn Martin, Lecturer of Epidemiology, Institute of Applied Health Sciences, University of Aberdeen kathryn.martin@abdn.ac.uk Lynn Laidlaw, Patient Partner. lynnlaidlaw0@gmail.com Fiona Talkington, Patient Partner Gordon Liddle, Patient Partner Jo Josh, Patient Partner
Statistician	Petra Rauchhaus, TCTU, University of Dundee p.rauchhaus@dundee.ac.uk

LIST of CONTENTS

I. LIST OF ABBREVIATIONS

BPI	Brief Pain Inventory
CI	Chief Investigator
CIPN	Chemotherapy Induced Peripheral Neuropathy
CRIF	Clinical Research Imaging Facility
DMS	Data Management System
DN4	Douleur Neuropathique en 4
ECOG	Eastern Cooperative Oncology Group
GCP	Good Clinical Practice
HIC	Health Informatic Services
ICF	Informed Consent Form
IDS-SR	Inventory of Depressive Symptomatology
ISRCTN	International Standard Randomised Controlled Trials Number
MDASI	Core MD Anderson Symptom Inventory
MI	Multiple Imputation
MRI	Magnetic Resonance Imaging
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NeuP	Neuropathic Pain
NHS R&D	National Health Service Research & Development
PI	Principal Investigator
PIS	Participant Information Sheet
PROMIS	Patient-Reported Outcomes Measurement Information System
QST	Quantitative Sensory Testing
REC	Research Ethics Committee
SAP	Statistical Analysis Plan
SIMD	Scottish Index of Multiple Deprivation
SMG	Study Management Group
SOP	Standard Operating Procedure
SOM-7	The 7-item State Optimism Measure
TCTU	Tayside Clinical Trials Unit
TIPI	Ten Item Personality Item
TNSc	Total Neuropathy Score clinical

II. STUDY SUMMARY

Study Title	**PAINSTORM: Partnership for Assessment and Investigation of NeuP: Studies Tracking Outcomes, Risks and Mechanisms**
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 Chemotherapy Induced Peripheral Neuropathy (CIPN) study being led by the University of Dundee: PAINSTORM Dundee CIPN Study	
Study Design	Observational, longitudinal
Study Participants	People receiving potentially neurotoxic chemotherapy
Planned Sample Size	200
Follow up duration	12 months
Planned Study Period	4 years
Objectives	Primary: Deep phenotyping approach to identify psychosocial, clinical and neurobiological factors that are associated with the development and/ or maintenance of painful or non-painful CIPN, as a result of neurotoxic chemotherapy for cancer. Secondary: Characterisation of Neuropathic Pain (NeuP) within CIPN cohort

III. FUNDING AND SUPPORT IN KIND

The Advanced Pain Discovery Platform – a 4-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.

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

The CI will be responsible for the conduct of the study. Site delegate(s) will oversee the study and will be accountable to the CI. A study-specific Delegation Log will be prepared detailing the duties of each member of staff working on the study.

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 Research Ethics Committee (REC). Appropriate NHS Research and Development (R&D) permission will be obtained prior to commencement of the study.

The study will be co-ordinated by a Study Management Group (SMG), to include the CI and co-investigators, Clinical Fellow, Senior Trial Manager, Research Nurse and Patient Partner(s). Minutes of the SMG will be maintained in the Trial Master File.

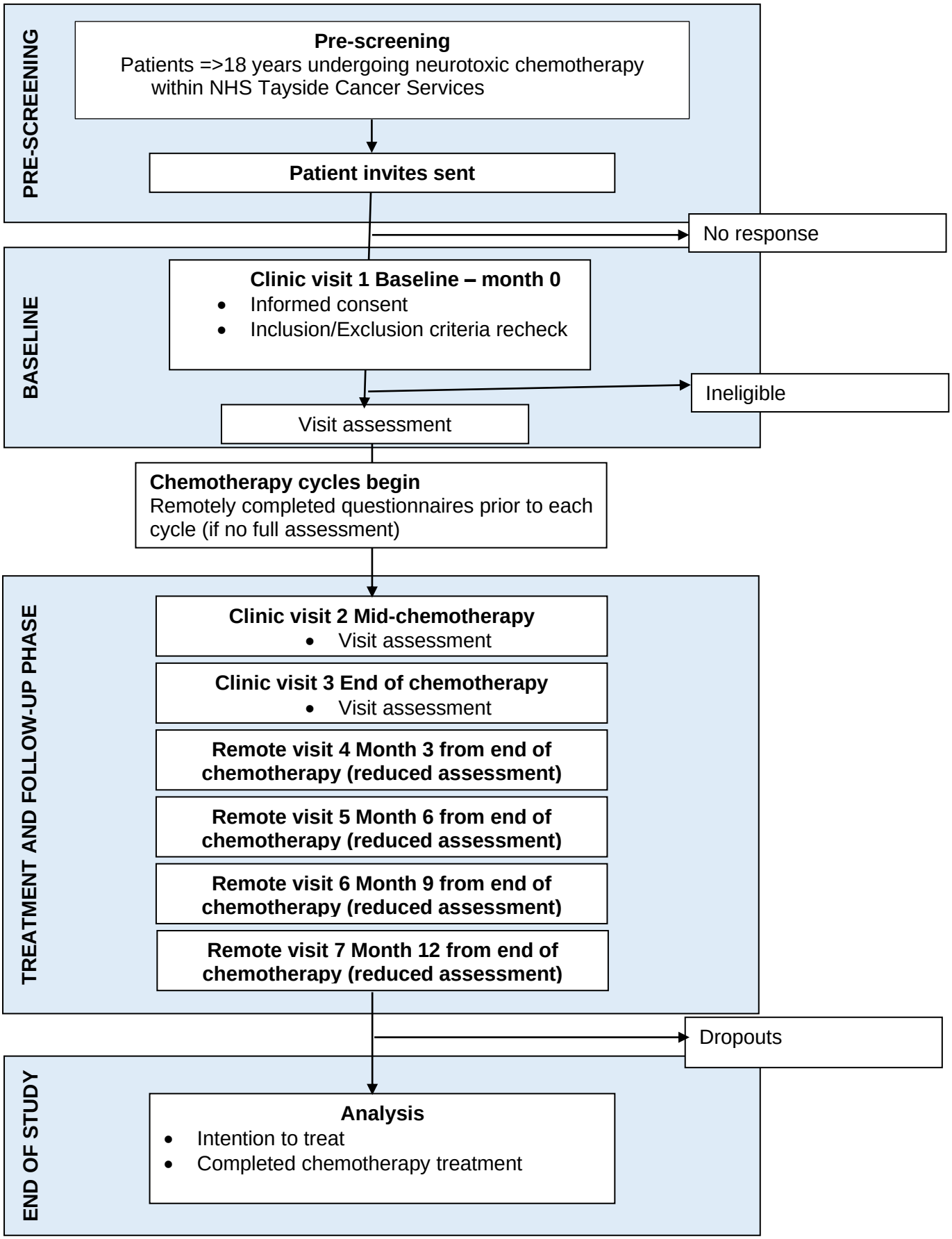
VI. PROTOCOL CONTRIBUTORS

Chief Investigator, Lesley Colvin: Draft, review and final approval
Co-investigator, Blair H. Smith: Initial draft, review
Co-investigator, Douglas Steele: Review
Senior Trial Manager, Margaret Band, Tayside Clinical Trials Unit (TCTU), University of Dundee: Re-draft and review
Clinical Fellow, Clare Clarke, TCTU, University of Dundee: Re-draft and review
Senior Research Statistician, Petra Rauchhaus, TCTU, University of Dundee: Review
Patient Partner, Lynn Laidlaw: Review
Patient Partner, Fiona Talkington: Review
Patient Partner, Gordon Liddle: Review
Patient Partner, Jo Josh: Review

VII. KEY WORDS

NeuP, genomics, epidemiology, neuropathy, chemotherapy induced peripheral neuropathy,

VIII. STUDY FLOW CHART



1. BACKGROUND

The PAINSTORM consortium is a collaboration of leading researchers in the field of neuropathic pain (NeuP), genomics, epidemiology and neuropathy, from the UK and Belgium, and Patient Insight Partners. The Patient Insight Partners are people living with NeuP, who have been involved in the design of the study since the pre-funding stage. We are aiming 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.

NeuP is caused by a lesion or disease of the somatosensory nervous system. NeuP is common, affecting 8-10% of the population. Crucially, not everyone with such an injury/ insult goes on to develop significant NeuP, and those who do develop it have a wide range of severity, impact, and outcomes. This variation in pain prevalence/severity involves a complex interaction between genetic, environmental and clinical factors. 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. The prevalence of NeuP is projected to increase due to an aging population, the diabetes/obesity epidemic and improved cancer survival. Unfortunately, the management of NeuP is inadequate due to poor efficacy and tolerability of current therapies. First-line therapy is usually analgesic medication, although psychological strategies and neuro-modulation may be applied in specialist settings.

Cancer incidence is rising (UK:>363,000 new cases/year), and projected to increase. Combined with improved survival (50% survive for >10 years), the number of people living with cancer, and/or its treatment-related adverse effects, is also projected to increase (cancerresearchuk.org). Unfortunately, many of the commonly used and effective chemotherapies (eg platinums, taxanes) can cause Chemotherapy Induced Peripheral Neuropathy (CIPN). This glove-and-stocking neuropathy presents with sensory dysfunction and pain as prominent features. CIPN can affect ~ 67% (or more) of patients during chemotherapy; ~33% will suffer long-term problems. It has a major impact on quality of life, and can be severe enough (pain/motor function) to require dose reduction or cessation of chemotherapy, potentially reducing survival. Current treatments for established painful CIPN are usually extrapolated from other neuropathic conditions, have limited efficacy, and often have unacceptable side effects. There are no proven therapies currently available for CIPN prevention. We do not fully understand why some people develop (painful) CIPN, and others do not, nor why it persists in some and not others.

As part of PAINSTORM, the University of Dundee is leading the CIPN study (PAINSTORM Dundee CIPN Study). This will involve recruitment of a cohort of people scheduled to receive potentially neurotoxic chemotherapy for cancer treatment, placing them at risk of CIPN. This study will use longitudinal deep phenotyping (including clinical, psychosocial and psychophysical factors), with assessments from pre-chemotherapy, during and after completion of chemotherapy. This will identify any onset and progression of neuropathy and pain, and factors that may be associated with this. Optional components of the study are blood analysis and/ or storage for potential CIPN biomarkers (e.g. neurofilament light chain) and genetic factors (storage) and up to 100 eligible participants will be sequentially offered magnetic resonance imaging (structural and functional).

2. RATIONALE

Major unmet needs for the field include: ability to predict CIPN; lack of preventive strategies; understanding how best to assess and individualise existing therapies; and improving translation from promising preclinical therapies to the clinic. Such translation requires better human cellular models, improved CIPN biomarkers and trial-ready stratified cohorts. The molecular, physiological and psychosocial factors underlying CIPN are too often studied in isolation and targeted as silos with a lack of consensus. Working with our patient partners on this project, there is clear agreement of the urgent need to better understand CIPN development, persistance, assessment and treatment.

2.1. Assessment and Management of Risk

In this observational study there is no risk from an intervention, however, people may find the detailed assessment process somewhat tiring or burdensome, especially at what can be a frightening and confusing time following a cancer diagnosis. We have previous experience of using this assessment approach successfully in this patient population and have also worked with patient partners to ensure that the proposed assessments are acceptable, with a range of approaches available to support participants.

Additionally, we are actively working with patient partners and relevant third sector organisations locally and nationally (e.g., Maggie's Centres, Tayside Cancer Support, and Egality UK) to maximise diversity of participants and address any barriers to participation in those who are seldom heard. We will provide additional support where necessary. For example, participants can elect to have a chosen "study partner" to help them with the study, if they wish, such as a friend or relative. Peer support through local charities will also be available, depending on participant preference.

If patients consent to having blood samples taken, there may be some discomfort, and possibly bruising from this. Quantitative Sensory Testing (QST) involves assessing participants sensation ability to feel skin temperature, touch and pressure changes. Participants may experience any uncomfortable stimulus on the skin during these assessments.

If participants agree to the wearing of an ActivPAL™ activity monitor, the ActivPAL™ will be attached to the skin on the thigh with hypoallergenic tape for a period of up to 7 days prior to starting chemotherapy, and in the week leading up to each face to face assessment (i.e. 3 times in total). If the participant reports any skin irritation, the ActivPAL™ activity monitor will be removed and appropriate clinical advice and care provided.

Optional Magnetic Resonance Imaging (MRI) assessment

One hundred participants (sequentially offered) can elect to participate in an optional neuroimaging component, using structural and functional MRI. These scans do not involve radiation. MRI uses a strong magnetic field and for safety reasons we need to identify metallic implants inside or outside the body that may be affected by the field. Participants will be closely assessed to ensure that it is safe for them to go into the MRI scanner. Participants will be assessed according to local procedures.

The total time for the scanning session is approx. 1 hour. Participants will be informed that the scanner is noisy and sometimes people find it uncomfortable being enclosed. Participants with

claustrophobia will be advised not to take part. Participants have access to a button which they can press to immediately terminate the scanning session if experiencing anxiety or discomfort.

Functional neuroimaging will be done followed by sensory and cognitive assessments as outlined in section 6.4 of the protocol. During the scan, QST stimuli are manually applied by an assistant in the scanner room (takes about 10 minutes). The procedure adheres to the Control of Electromagnetic Forces At Work regulations to ensure safety for all participants and staff involved. During these scans participants may experience a mildly uncomfortable stimulus on the skin, the same as occurs during routine QST outside the scanner. Participants will then be asked to complete a task which involves playing a game to maximise winning (takes about 10 minutes). This helps us understand the role of the reward systems in the brain, which may be involved in pain processing. Participants are able to see pictures on a screen during scanning and make decisions using button presses.

Images will be review by a radiologist for incidental findings reporting. If clinically significant abnormalities are reported then this will be discussed with the treating clinical team and the participant.

3. OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

3.1. Hypothesis

An individual's risk of developing acute or chronic CIPN 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. PAINSTORM Dundee CIPIN Study will contribute to this, by generating a new, deeply phenotyped cohort of people undergoing potentially neurotoxic chemotherapy.

3.3. Primary objective

Use of a deep phenotyping approach to identify psychosocial, clinical and neurobiological factors that are associated with the development and/ or maintenance of painful or non-painful CIPN, as a result of neurotoxic chemotherapy for cancer.

3.4. Secondary objectives

To characterise NeuP and its impact within a CIPN cohort. These data will be integrated with other relevant PAINSTORM work packages to produce a high-quality longitudinal dataset.

3.5. Table of Endpoints and outcomes:

Timepoints: Face to face assessments at baseline, mid-chemotherapy, end of chemotherapy (timing depends on chemotherapy schedule), with all detailed measures. Note: Blood sampling MRI and use of physical activity monitor are optional (participant preference); MRI will be

offered to 100 eligible participants sequentially. Participants will complete a reduced questionnaire set prior to every cycle of chemotherapy. This can be completed remotely (paper/ email/ telephone/ online) according to participant preference. Pain measures are only completed if pain is present.

Objectives	Outcome Measures	Timepoints measured
Primary		
Development (or persistence) of painless or painful CIPN	• EORTC-CIPN20 ○ Change in chemotherapy/dose reduction due to neurotoxicity.	• Baseline, mid and end of chemotherapy 3, 6, 9 and 12 months after completion of chemotherapy.
	• Pain location: List of body sites / Body map.	• Baseline, mid and end of chemotherapy 3, 6, 9 and 12 months after completion of chemotherapy.
	• Total Neuropathy Score clinical (TNSc)	• Baseline, mid and end of chemotherapy.
Pain severity	• Chronic Pain Grade • Brief Pain Inventory (BPI) Numeric Rating Scale (average in last 24 hours)	• Baseline mid and end of chemotherapy at 3, 6, 9 and 12 months after completion of chemotherapy.
Secondary		
Lifestyle	• Eastern Cooperative Oncology Group (ECOG) Performance Status Scale	• Baseline, mid and end of chemotherapy
	• Any changes to planned oncological treatment	• Baseline, mid and end of chemotherapy
	• Past medical History/ co-morbidities Family History Details of cancer type and stage Oncological treatment including planned chemo protocol (*and any changes to this with reasons*) Duration of CIPN Smoking questionnaire Alcohol questionnaire Illicit drugs	• Baseline
	• Concomitant medication	• Baseline, mid and end of chemotherapy at 3, 6, 9 and 12 months after

		completion of chemotherapy.
	• Physical function: Saltin-Grimby Physical Activity Level Scale	• Baseline, mid and end of chemotherapy at 3, 6, 9 and 12 months after completion of chemotherapy.
	• Step count (ActivPAL™ accelerometer)	• Baseline, mid and end of chemotherapy
	• Patterns of daily living (time spent sitting, standing, stepping and lying) using ActivPAL™ accelerometer.	• Baseline, mid and end of chemotherapy
Demographics	• Age • Sex • Scottish Index of Multiple Deprivation (SIMD) • Weight • Height • Years in full-time education • Working status • Household income	• Baseline
Neurological impact	• National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v5. (sensory and motor)	• Baseline, mid and end of chemotherapy at 3, 6, 9 and 12 months after completion of chemotherapy.
	• Quantitative Sensory Testing	• Baseline, mid and end of chemotherapy
	• Grooved pegboard	• Baseline, mid and end of chemotherapy
	• Brain structure and function (Magnetic Resonance Imaging)	• Baseline and end of chemotherapy.
Clinical	• Blood/ serum biomarkers	• Baseline, mid and end of chemotherapy.

Type and quality of pain	• Douleur Neuropathique en 4 (DN4) • NeuP Symptom Inventory (12 items)	• Baseline, mid and end of chemotherapy at 3, 6, 9 and 12 months after completion of chemotherapy.
Quality of Life	• EQ-5D-5L21 • Brief Pain Inventory (BPI) Pain interference • Core MD Anderson Symptom Inventory (MDASI)	• Baseline, mid and end of chemotherapy at 3, 6, 9 and 12 months after completion of chemotherapy.
Psychological Health	• Patient-Reported Outcomes Measurement Information System (PROMIS): Depression; Anxiety; Sleep; Support • Trauma • Pain Catastrophizing Scale • Inventory of Depressive Symptomatology (IDS-SR) • The 7-item State Optimism Measure (SOM-7) • Ten Item Personality Inventory (TIPI)	• Baseline, mid and end of chemotherapy at 3, 6, 9 and 12 months after completion of chemotherapy.

4. STUDY DESIGN

Observational study of a longitudinal prospective cohort of people receiving potentially neurotoxic chemotherapy for cancer, placing them at risk of CIPN. This study will assess participants at baseline and during and after treatment, to determine any onset and progression of neuropathy and pain, and factors that may be associated with this.

5. STUDY SETTING

Single Centre (NHS Tayside). Study activities will be carried out mainly in the Stefani Unit and the Clinical Research Imaging Facility (CRIF), at Ninewells Hospital, Dundee. The Stefani Unit and CRIF are both clinical research facilities which provide clinical space and expert staff to support patients with cancer who are taking part in clinical research studies. Other facilities within NHS Tayside/ use of technology to minimise travel, as preferred by participant, may be used if thought to be more appropriate for a particular participant or group of participants.

6. PARTICIPANT ELIGIBILITY CRITERIA

6.1. Inclusion criteria

- 18 years or older

- Planned course of potentially neurotoxic chemotherapy for the treatment of cancer. This includes the following:
    - Platinum drugs
    - Taxanes
    - Vinca alkaloids
    - Epothilones
    - Proteasome inhibitors
    - Thalidomide
    - Vedotin-based drugs
    - Checkpoint inhibitors

6.2. Exclusion criteria

- Incapacity to give consent or to complete the study questionnaires due to insufficient language command or mental deficiencies, in the opinion of the investigator.
- Functional impairment - ECOG Performance Status Scale great than or equal to 3 at baseline.
- Concurrent clinically defined severe physical or psychiatric disorders that would preclude accurate phenotyping.
- Moderate to severe pain from other causes that may confound assessment or reporting of pain if unable to differentiate from CIPN.
- Patients who are in the opinion of the investigator, or treating oncology team, unsuitable for participation in the study.

7. STUDY PROCEDURES

7.1. Recruitment

7.1.1. Participant identification

Potential participants being treated within NHS Tayside Cancer Services will be identified by members of the clinical care team and, if potential participants agree, they will be given a participant information sheet (PIS) /invitation letter at clinic. Initial contact will be by the clinical care team or local clinician. The PIS and invitation letter may also be posted out or emailed, prior to attending for pre-chemotherapy assessment. Postage or email of invitation letters and PIS will be carried out by the Principal Investigator (PI) or delegated research team member. Participants will already have had an appointment with their oncologist, will have a cancer diagnosis with discussion of risks/ benefits of oncological treatment options and a chemotherapy treatment plan agreed prior to attending clinic for pre-chemotherapy assessment. Feedback from local patient partners suggested this appointment would be a good time for the participant to ask questions about the study and consider taking part as the participant is both aware of the diagnosis and has agreed to chemotherapy. It also it is important in terms of timing; the baseline assessments (including MRI scan for some) need scheduling and completing before chemotherapy begins. If the participant has had the study information for at least 24 hours before they attend for pre-chemotherapy assessment; they could potentially participate in the study that day if they so wished which would prevent them from needing to return another day for the study assessments. This timing is of particular importance during the pandemic when

attendance to hospital should be minimised to avoid risk of Covid infection. If participants prefer to split baseline assessments over different appointments prior to starting chemotherapy; this will be organised by the PI or delegate and will not be considered as an extra visit.

When first contact is via a letter, a PIS will also be sent. Participants will be asked to contact the research team if they are interested in the study. When first contact is in a hospital clinic they will be given a PIS and will be asked to either return an expression of interest in a stamped addressed envelope or to contact a member of the research team by telephone or email. Contact details will be provided on the PIS. Study staff may also arrange a convenient time with the participant to call them to see if they wish to take part, discuss any concerns and additional support that they might need.

Should individuals express an interest in taking part in the study, the PI or delegate will contact the individual and ask if they give permission to check their medical notes. Individuals who return a reply slip should have provided this permission on the slip in which case further contact with them would not be required prior to accessing their medical notes.

Recruitment may also utilise publicity materials including posters, information leaflets, social media, video and/or advertisements, which will be developed with patient partners. These will be submitted for regulatory approval as they are developed.

The PI will be responsible for recruitment but may delegate to other named individuals within the study team.

7.1.2. Pre-Screening

Potential participants will be pre-screened by a member of the research team to check they are potentially eligibility.

7.1.3. Ineligible participants

Where an individual is found to be ineligible for study participation, they will be thanked and the reasons for the ineligibility fully explained. Any questions will be answered by an appropriate member of the research team.

7.2. Payment

Travel expenses for any visits additional to normal care will be given. Appropriate subsistence/ costs will be covered or provided.

7.3. Consent

The PI has overall responsibility for the study, this includes the taking of informed consent of participants. They will ensure that any person delegated responsibility to participate in the informed consent process is duly authorised, trained and competent to participate according to the ethically approved protocol, principles of GCP and Declaration of Helsinki.

Informed consent will be obtained prior to the participant undergoing procedures that are specifically for the purposes of the study and are out-with routine clinical care.

The right of a participant to refuse participation without giving reasons will be respected.

The participant will remain free to withdraw at any time from the study without giving reasons and without prejudicing his/her further treatment and will be provided with a contact point where he/she may obtain further information about the study. Data and samples collected up to the

point of withdrawal will be used unless a participant expresses that they do not want their data and/or samples to be used.

Interested individuals will be provided with a PIS before they are scheduled to attend their first research visit. They will be given at least 24 hours to consider their participation in the study. A visit will be arranged by the PI or delegate and participant for a mutually convenient time where there will be a discussion between the potential participant and a trained member of the research team, knowledgeable about the nature and objectives of the study and possible risks associated with participation. Participants will be able to ask any questions about the study. We have had extensive discussions with patient partners to maximise diversity of participants, aiming to reduce barriers to participation. Where possible, we will offer additional support if needed (e.g. study partner, IT resource, third sector input). If they decide to participate, written informed consent will be obtained.

The original Informed Consent Form (ICF) will be filed in the Study Master File (SMF) and a copy will be given to the participant and a copy will be saved in the participant's medical notes.

For adults who lose capacity their previous wishes will remain valid unless the protocol changes significantly. If this occurs and further consent is required from a participant who has lost capacity, an appropriate person will be asked for their consent. This will be fully documented in the patient's notes. In all cases the PI or delegate will consult with carers and take note of any signs of objection or distress from the participant – the participant will be withdrawn if they raise objection. Where appropriate the participant will be withdrawn from any further assessments and agreement will be sought from a carer to allow data collection.

7.4. Screening

Eligibility against the inclusion and exclusion criteria will be checked by a delegated member of the research team. This will include assessment of functional impairment using the ECOG Performance Status Scale.

7.5. Study assessments

Appendix 1 (Section 13.1) shows the schedule of procedures.

The study team will prioritise assessments asking participants to complete as many as they feel able to at that visit, with the option of completion at a further visit, or of postal/ email/ online return for those parts of the assessment not requiring face to face input. Where possible, additional support with completing questionnaires e.g. for visually impaired, English is not first language, will be offered to maximise diversity, and reduce participation barriers where necessary.

PAINSTORM Dundee Questionnaire

A web-based version of the PAINSTORM Dundee questionnaire will be developed by Health Informatic Services (HIC), University of Dundee, this will be based on a modification of the previously used DOLORisk questionnaire (see Pascal et al 2019) and include:

Demographics: Age, gender, weight, height, years in education and working status, SIMD.

Past Medical History

- Co-morbidities (past and present)

- Concomitant medication
- Family History
- Cancer
- Details of cancer type and stage
- Oncological treatment including planned chemo protocol (*and any changes to this with reasons*)

Characterisation of pain:

- EORTC-CIPN20
- BPI (including interference subscale).

Intensity of the pain:

- Chronic Pain Grade
- BPI (intensity subscale)

Neuropathic descriptors:

- DN4 questions
- NeuP Symptom Inventory

Pain location:

- List of body sites
- Body map

Psychological and psychosocial:

- PROMIS (includes depression, anxiety, sleep, support
- Trauma questionnaire.
- MDASI
- IDS-SR
- EQ-5D-5L21
- Pain Catastrophizing Scale
- SOM-7
- TIPI

Lifestyle:

- Smoking
- Alcohol
- Saltin-Grimby Physical Activity Level Scale
- Grooved pegboard test
- Step count (ActivPAL™ accelerometer)
- Patterns of daily living (time spent sitting, standing, stepping and lying) using ActivPAL™ accelerometer.

Clinical examination

- NCI-CTCv5. (sensory and motor).
- QST**:** this is a measure of sensory perception in response to defined sensory stimuli. QST is performed according to a modification of the previously published protocol of the German Research Network on NeuP and is harmonised across the PAINSTORM consortium. We have previous experience of using QST in a similar patient population (Scott, Colvin et al 2012). There will be an option for a reduced QST protocol to assess mechanical (touch, pressure) and thermal sensation (warm/ hot; cool/ cold) if individual participants do not wish to undergo the more comprehensive assessment.
- TNSc is used for chemotherapy-induced neuropathy.
- The spatial extent of sensory deficits and sensory hypersensitivity will be recorded on a body map.

Blood samples:

Visit 1 – approx. 30ml

- Serum for neurofilament light chain and other potential biomarkers analyses
- Whole blood for storage for genetic analysis

Visits 2 & 3 – approx. 20 ml

- Serum for neurofilament light chain and other potential biomarkers analyses

Samples will be collected, processed and stored for future research. They will be stored by the Tayside Biorepository, with a portion of the serum being transferred to Imperial College London for planned biomarker analysis.

MRI: Magnetic Resonance Imaging

PAINSTORM Dundee CIPN Study has funding for a total of 200 scans. Sequential, eligible patients will be offered the opportunity to participate in this optional part of the study. Within funding constraints each participant will be scanned at baseline (before starting chemotherapy), and again after completion of chemotherapy. The aim of the neuroimaging investigation is to

i) identify brain structural and functional changes associated with development of CIPN
ii) identify brain structural and functional measures from the baseline scans that predict later development of CIPN.

All scanning will be done at the CRIF, Ninewells Hospital, following SOPs:

i) Participants will receive standard high resolution brain structure scans (T1, T2 and Flair) which will be used for both neuroimaging analyses. (15 min).
ii) Functional neuroimaging will then be done during which QST (see below) stimuli are manually applied by an assistant in the scanner room (10 min). Participants then take part in a task which involves playing a game to maximise winning (10 min) During both periods, participants are able to see pictures on a screen during scanning and make decisions using button presses.
iii) After this diffusion tensor imaging data will be acquired which takes about 10 min.
iv) Finally resting state fMRI data will be acquired (10 min).

The total time for the scanning session is about 1 hour. The CRIF staff have extensive experience of care of participants in a scanning environment. When in the scanning room, participants will have access to a button, which they can press to immediately terminate the scanning session if they wish to.

Images will be reviewed by a radiologist for incidental findings reporting. If clinically significant abnormalities are reported then this will be discussed with the treating clinical team and the participant.

Wearable Technology

ActivPal™ accelerometers to collate measures of physical function including step count, patterns of daily living (*time spent sitting, standing, stepping and lying*) will be offered to participants (optional). Participants will be asked to wear them in the week prior to the first cycle of chemotherapy, mid-way and at the end of their chemotherapy.

7.6. 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.

7.7. Withdrawal criteria

All participants are free to withdraw at any time and are not obliged to give reason(s). The PI or delegate will make a reasonable effort to ascertain the reason(s), both for those who express their right to withdraw and for those lost to follow up, while fully respecting the individual's rights. The investigator may withdraw a participant at any time if it is in the best interest of the participant.

If a participant withdraws, or is withdrawn, their data and any research tissue 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 provided, including the reasons for their loss, if known, and its relationship to treatment and outcome.

7.8. Storage and analysis of clinical samples

Serum will be collected for neurofilament light chain and other potential biomarker analysis. A portion of this serum will be centrally stored within Tayside Biorepository on a short-term basis prior to being transferred to Imperial College London where biomarker analysis shall be completed. An accredited courier e.g., Marken will be used by the Biorepository to ensure safe frozen transport of samples.

Surplus blood (and serum) samples will be stored for future research use. Samples will be stored within appropriate secure, alarmed freezers within the research lab and samples will be registered with Tayside Biorepository. Alternatively, where there is capacity Tayside Biorepository will be used to store surplus study samples within their own freezers. Future use of surplus samples will be governed via the Tayside Tissue Access Committee to provide delegated ethical approval subject to the conditions of consent.

Excess biological samples originating from Tayside that are being taken for clinical reasons may be stored for future use if no longer required for clinical purposes. The research team will work with the biorepository and the appropriate clinical teams to ensure appropriate interception of these samples so that de-identification, processing and storage can be carried out in accordance with the Scottish Human Tissue Accreditation Scheme.

Surplus samples originating from Tayside participants that require biobanking will be pseudo-anonymised. This will therefore allow the biorepository or associated research fellow to work with the Health Informatics Centre to associate data with the sample and securely transfer the data to a researcher for future use after receiving delegated ethics.

7.9. End of study

The end of study is defined as last participant, last visit. The Sponsor and/or PI 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 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

8.1. Sample size calculation

The sample size of n=200 will provide a robust, high- quality dataset of deeply phenotyped participants for use in PAINSTORM and beyond. The neuroimaging component will be one of the biggest to date in this patient population.

8.2. Planned recruitment rate

We estimate that recruitment of 200 participants is expected to be completed within approximately 30 months (i.e. at a rate of ~ 2 participants per week). Pre-funding work with people with lived experience of undergoing chemotherapy, combined with known new patient numbers in Tayside Cancer Service indicate that this is a realistic target recruitment rate.

8.3. Statistical analysis plan

A statistical analysis plan (SAP) will be prepared and finalized prior to database lock and final analysis.

8.4. Participant population

The participant populations will be on an Intention-to-treat basis of participants with at least one round of chemotherapy. A complete cases analysis may be added for specific outcomes. This will be defined in the SAP.

8.5. Statistical analysis of clinical data

For the primary analysis, participants will be classified as having a neuropathic or non-neuropathic component, based on their phenotype. Neuropathic phenotypes will be defined as a change of at least 2 on the sensory subscale of the EORTC-CIPN20 questionnaire and/ or dose reduction/ cessation of chemotherapy at any time during the chemotherapy. The primary analysis will be performed on the basis of these two groups. This definition may be modified as

PAINSTORM Work package 2 evolves, which focuses on improving assessment to better reflect the experience of people living with NeuP(see 8.7). 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 NeuP group and an additional column for the total population relevant to that table/treatment, including any missing observations.

The primary analysis will examine the factors which predict the classification into the two groups and aim to establish a prediction model.

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

The extent of missing data will be examined and the reason for missingness ascertained. Multiple imputation (MI) may be used to impute missing values if necessary and where assumptions for missing at random data are met.

8.7. Other statistical considerations.

One of the PAINSTORM work packages aims to establish patient centred outcomes and disease classification which may be more important to the patient groups. As that work package is not completed, those outcomes are not currently available. It is expected that the work package will create results prior to the analysis of this study, and an iterative approach will be used to ensure that outcome measures are meaningful to people living with the condition. Any important findings from the work package will be included in the SAP and run as an exploratory analysis.

9. DATA MANAGEMENT

9.1. Data collection tools and source document identification

Imaging data will be pseudo-anonymised with a code, extracted from the scanner then stored on the University of Dundee Life Sciences Compute Cluster for backup and analyses. Statistical analyses will be done using standard neuroimaging computational methods: e.g. Matlab, Statistical Parametric Maps, FSL, Freesurfer, R. The data will be stored and backed up in the Life Sciences Compute Cluster , University of Dundee and analyses done there, the other will go to HIC for the ALLEVIATE data hub or equivalent.

Questionnaires will be returned to HIC using the pseudo-anonymised study code for identification, where data will be entered on the study database, managed by HIC.

Medical records/ study questionnaires will be used as source data. All study data relevant to a participant’s general medical history will be recorded in the medical records. Essential information regarding study participation will also be recorded in the medical records.

Details of datasets transfer, storage and analysis will be documented in the Data Management Plan.

9.2. Data handling and record keeping

Data will be stored in the Health Informatics Centre (HIC), and the Life Sciences Compute Cluster, University of Dundee. HIC has access-controlled data server rooms contain 2 separate networks which hold all identifiable NHS data or University research data; this facility is only accessible to HIC staff who have provided a Disclosure Scotland security certification and have completed a confidentiality agreement. Industry standard login access controls are in place across all HIC infrastructure, in line with University of Dundee best practice. HIC facilities and processes are audited at least once annually by external auditors as part of the HIC ISO27001 certification.

Data management will be undertaken in close collaboration with HIC Services who will develop the Data Management System (DMS). An anonymised copy of neuroimaging data, pain and psychological ratings data, will also be stored in the secure Life Sciences Compute Cluster where the computationally intensive neuroimaging analyses will be carried out. The DMS will be based on the protocol for the study. 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 PAINSTORM data will be housed in Alleviate (Advanced Pain Discovery Platform Data Hub), within HIC as a resource for the wider pain research community, subject to appropriate data governance measures. The DMS 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 PI.

Development and validation of the study DMS, quality control and extraction of data will be done according to local SOPs. Extracts for analysis will be managed by the PI.

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. Medical notes will be maintained in compliance with local NHS Policy on Retention of Medical Case notes.

10. AUDIT & INSPECTION

The CI, PI 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, ICFs 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 Study 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 CI will notify the REC of the end of the study. If the study is ended prematurely, the CI will notify the REC, including the reasons for the premature termination

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

11.2. Peer review

Extensively reviewed by the funders (UK Research and Innovation/ Versus Arthritis/ Eli Lilly, co-ordinated by Medical Research Council with external peer review) as part of the award process.

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 people have volunteered to be patient partners for PAINSTORM Dundee on the main research team, all of whom have also been involved throughout the pre-funding stage. The protocol has been reviewed by some of the patient partners. Patient partners are invited to attend REC meetings so that they can describe what is being done with patients in patient/public facing materials (eg information leaflets). All information material, such as PISs 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 are integral members of the SMG 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.

We are working with relevant third sector organisations (Maggie's Centre, Tayside Cancer Support, CanDu) to reduce barriers to participation and provide additional support when required.

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/PI 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 Breach Log and reported to Sponsor via the breach reporting process.

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 Data Protection Act 2018 and General Data Protection Regulation. 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, and committee members for the overall study management

The SMG will aim to identify and disclose any competing interests that might influence study design, conduct, or reporting of results.

11.9. Indemnity

The University of Dundee are sponsoring this single centre 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 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 PI and Study Statistician will have access to the final study dataset. Access to the final study dataset to others will be approved by the PI.

12. DISSEMINIATION 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 active members 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. 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

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.

13. REFERENCES

1 Treede RD, Jensen TS, Campbell JN, Cruccu G, Dostrovsky JO, Griffin JW, et al. NeuP: redefinition and a grading system for clinical and research purposes. *Neurology*. 2008 **70** 1630-5.

2 von Hehn CA, Baron R, Woolf CJ. Deconstructing the NeuP phenotype to reveal neural mechanisms. *Neuron* 2012 **73** 638-52.

3 Bouhassira D, Lanteri-Minet M, Attal N, Laurent B, Touboul C. Prevalence of chronic pain with neuropathic characteristics in the general population. *Pain* 2008 **136** 380-7.

4 Torrance N, Smith BH, Bennett MI, Lee AJ. The epidemiology of chronic pain of predominantly neuropathic origin. Results from a general population survey. *Journal of Pain* 2006 **7** 281-9.

5 http://diabetesgenetics.dundee.ac.uk/

6 Van Hecke O, Austin S, Smith BH, Khan R, Torrance N. NeuP in the general population: a systematic review of epidemiological studies. *Pain* 2014 **155** 654-62

7 Meng W, Deshmukh HA, van Zuydam NR, Liu Y, Donnelly LA, Zhou K, Morris AD, Colhoun H, Palmer CNA, Smith BH. A genome-wide association study suggests an association of Chr8p21.3 (GFRA2) for diabetic NeuP. *European Journal of Pain* 2015 **19** 392-9.

8 Smith BH, Campbell A, Linksted P, McGilchrist MM, Wisely L, Fitzpatrick B, Ford I, Hocking LJ, Jackson C, Kerr SM, Lindsay RS, Morton R, Palmer CAN, Deary IJ, Macintyre DJ, Campbell H, Dominiczak AF, Porteous D, Morris AD. Cohort profile. Generation Scotland: Scottish Family Health Study (GS:SFHS). The study, its participants, and their potential for genetic research on health and illness. *International Journal of Epidemiology* 2013 **42** 689-700.

9 Smith BH, Torrance N, Ferguson JE, Bennett MI, Serpell MG, Dunn KM. Towards a definition of refractory NeuP for epidemiological research. An international Delphi survey of experts. *BMC Neurology* 2012 **12** 29

10 Van Hecke O, Kamerman P, Attal N, Baron R, Bjornsdottir G, Bennett DL, Bennett MI, Bouhassira D, Diatchenko L, Freeman R, Freynhagen R, Haanpää M, Jensen TS, Raja SN, Rice ASC, Seltzer Z, Thorgeirsson TE, Yarnitsky D, Smith BH. NeuP phenotyping by international consensus (NeuroPPIC): a NeuPSIG systematic review, Delphi survey and expert panel recommendations. Submitted to *Pain*

11 Bennett M, Smith BH, Potter J, Torrance N. The S-LANSS score for identifying pain of predominantly neuropathic origin: validation for use in clinic and postal research. *Journal of Pain* 2005 **6** 149-58.

12 Von Korff M, Ormel J, Keefe FJ, Dworkin SF. Grading the severity of chronic pain. *Pain* 1992 **50** 133-49.

13 Smith BH, Penny K, Purves A, Munro C, Smith WC, Grimshaw J, Wilson B, Chambers WAC. The Chronic Pain Grade questionnaire: acceptability and validity in postal research. *Pain* 1997 **71** 141-7.

14 Purves AM, Penny KI, Munro C, Smith BH, Grimshaw J, Wilson B, Smith WC, Chambers WA. Defining chronic pain for epidemiological research - assessing a subjective definition. *The Pain Clinic* 1998 **10** 139-47.

15 International Association for the Study of Pain. Classification of chronic pain. *Pain* 1986 **3** S1-S225.

16 EuroQoL Group. EuroQoL-a new facility for the measurement of health-related quality of life. *Health Policy* 1990 **16** 199-208.

17 Torrance N, Ferguson J, Afolabi E, Bennett MI, Serpell MG, Dunn K, Smith BH. NeuP in the community: more under-treated than refractory? *Pain* 2013 **154** 690-99.

18 HTTPS://WWW.CANCERRESEARCHUK.ORG/HEALTH-PROFESSIONAL/CANCER-STATISTICS-FOR-THE-UK

19 Gewander et al 2018 Trial designs for chemotherapy-induced peripheral neuropathy prevention: ACTTION recommendations - PubMed (nih.gov) https://pubmed.ncbi.nlm.nih.gov/30054438/

20 Scott AC, McConnell S, Laird B, Colvin L, Fallon M. Quantitative Sensory Testing to assess the sensory characteristics of cancer-induced bone pain after radiotherapy and potential clinical biomarkers of response. Eur J Pain. 2012 Jan;16(1):123-33. doi: 10.1016/j.ejpain.2011.05.002. PMID: 21658980.

21 Pascal MMV, Themistocleous AC, Baron R, Binder A, Bouhassira D, Crombez G, Finnerup Nb, Gierthmühlen J, Granovsky Y, Groop L, Hebert Hl, Jensen Ts, Johnsen K, Mccarthy Mi, Meng W, Palmer Cna, Rice Asc, Serra J, Solà R, Yarnitsky D, Smith Bh, Attal N, Bennett Dlh. Dolorisk: Study Protocol for a Multi-Centre Observational Study to understand the Risk Factors and Determinants of Neuropathic Pain. Wellcome Open Res. 2019 Feb 1;3:63. Doi: 10.12688/Wellcomeopenres.14576.2. Pmid: 30756091; Pmcid: Pmc6364377.

14. APPENDICIES

14.1. Appendix 1 – Schedule of Procedures

	V1[a]	V2[a]	V3[a]	V4[b]	V5[b]	V6[b]	V7[b]
				Follow up post chemo			
	Screen & Baseline	Mid Chemo	End of Chemo	3 months	6 months	9 months	12 months
	In clinic/ face to face			Postal/online/telephone			
Informed Consent	X						
ECOG Performance Status Scale	X	X	X				
Disease progression and alterations in oncological treatment plan	x	x	x	x	x	x	x
Eligibility	X						
Medical History	X						
Concomitant medications	X	X	X	X	X	X	X
Lifestyle (inc smoking, alcohol, ilicit drugs)	X						
Height and weight	X						
ActivPAL™ physical activity monitor[d]	X	X	X				
Demographics	X						
NCI CTCAE/AE	X	X	X				
QST	X	X	X				
Grooved pegboard test	X	X	X				
MRI scanning	X		X				
Research Bloods	X	X	X				
EORTC CIPN 20[ce]	X	X	X	X	X	X	X
List of body sites/body map[ce]	X	X	X	X	X	X	X
TNSc[c]	X	X	X				
Chronic Pain Grade[ce]	X	X	X	X	X	X	X
BPI[ce]	X	X	X	X	X	X	X

DN4 questions[e]	X	X	X	X	X	X	X
NeuP Symptom Inventory[e]	X	X	X	X	X	X	X
	V1[a]	**V2[a]**	**V3[a]**	**V4[b]**	**V5[b]**	**V6[b]**	**V7[b]**
EQ-5D-5L21	X	X	X	X	X	X	X
MDASI[e]	X	X	X	X	X	X	X
PROMIS	X	X	X	X	X	X	X
Pain Catastrophizing Scale	X	X	X	X	X	X	X
IDS-SR	X	X	X	X	X	X	X
SOM-7	X	X	X	X	X	X	X
TIPI	X	X	X	X	X	X	X
Saltin-Grimby Physical Activity Level Scale	X	X	X	X	X	X	X

Any of the visits may be carried out over more than one day if participants wish.

[a] Visits 1,2 and 3 will not be on the same timescale for all patients as the visits are tailored to the patient's individual chemotherapy schedule.

[b] Visits 4-7 will aim to be completed within 1 month either side of scheduled clinical appointments and according to patient preference. There will be no visit windows and it will not be considered a breach of protocol if visits are missed.

[c] Participants will fill in pain questionnaires only if they have pain.

[d] If participant has opted for an ActivPal™, they will wear that for the week prior to the cycles of chemotherapy where a face-to-face assessment is planned.

[e] Completed remotely (paper/ online/ telephone) prior to each cycle of chemotherapy if no face-to face visit is planned.

14.2. Appendix 2 – Amendment History

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