Interleukin-1 receptor antagonist treatment for refractory complex regional pain syndrome

INCA

INCA Protocol
V8.0, 22/05/2024

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Study Sponsor:
The University of Liverpool, Clinical Directorate
Thomas Yates Building
The Quadrangle, Brownlow Hill
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Study Funder: The Edelman Foundation

UNIVERSITY OF LIVERPOOL

Protocol Approval

I, the undersigned, hereby approve this clinical study protocol:

Authorised by Chief Investigator:

Signature: 

Date: 24 Jun 2024

Dr Andreas Goebel
Consultant in Pain Management

I, the undersigned, hereby approve this clinical study protocol:

Authorised on behalf of Sponsor:

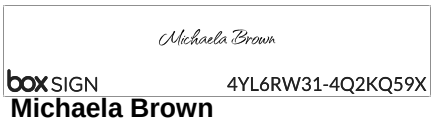
Signature: 

Date: May 23, 2024

Mrs Karen Jennings-Wilding
Senior Clinical Research Governance Manager

I, the undersigned, hereby approve this clinical study protocol:

Authorised on behalf of the Lead Statistician:

Signature: 

Date: 18 Jun 2024

Michaela Brown
Lead Statistician

General Information

This document describes the INCA trial including detailed information about procedures and recruitment. The protocol should not be used as an aide-memoir or guide for the treatment of other patients. Every care was taken in its drafting, but corrections or amendments may be necessary. Any amendments will be circulated to the investigators participating in the trial, but sites entering patients for the first time are advised to contact the coordinating centre (Liverpool Clinical Trials Centre (LCTC)) to confirm they have the most up-to-date version. Clinical problems relating to this trial should be referred to the relevant Chief Investigator (CI), Mr Andreas Goebel, via the LCTC.

This protocol defines the participant characteristics required for study entry and the schedule of treatment and follow-up. Participant recruitment will be undertaken in compliance with this document and applicable regulatory and governance requirements. Waivers to authorise non-compliance are not permitted.
Incidence of protocol non-compliance whether reported prospectively (e.g. where a treatment cannot be administered on a scheduled date as a result of public holidays) or retrospectively noted (e.g. as a result of central monitoring) are recorded as protocol deviations. These are monitored and reported to trial oversight committees.

The template content structure is consistent with SPIRIT (Standard Protocol Item: Recommendations for Interventional Trials 2013) and has regard for the Health Research Authority (HRA) guidance. Regulatory and ethical compliance information is located in section 16.

The LCTC has achieved full registration by the UK Clinical Research Collaboration (www.ukcrc.org) as their standards and systems were assessed by an international review panel as reaching the highest quality. The LCTC has a diverse trial portfolio underpinned by methodological rigour, a GCP-compliant data management system, and quality management system.

Contact Details: Institutions

Sponsor	Trial Management, Monitoring and Analysis	Clinical Laboratory
University of Liverpool Clinical Directorate Thomas Yates, The Quadrangle Brownlow Hill **Liverpool,** L3 5RB Tel no: 00 44 (0) 7717 863747 E-mail: Sponsor@liverpool.ac.uk	LCTC 1st Floor, Block C Waterhouse Building 1-3 Brownlow Street **Liverpool,** L69 3GL Tel. no: 0151 795 7795 E-mail: inca@liverpool.ac.uk	Andy Cross Clinical Sciences Centre 3rd Floor Rheumatology Laboratories University Hospital Aintree Longmoor Lane **Liverpool**,L9 7AL E-mail: across@liverpool.ac.uk
Statistics	**Trial Manager**	
LCTC 1st Floor, Block C Waterhouse Building 1-3 Brownlow Street Liverpool L69 3GL Tel no: 0151 795 7795 Email: inca@liverpool.ac.uk	LCTC 1st Floor, Block C Waterhouse Building 1-3 Brownlow Street Liverpool L69 3GL Tel. no: 0151 795 7795 Email: inca@liverpool.ac.uk	

Contact Details: Individuals

Individual Authorised to Sign the Protocol and Protocol Amendments on behalf of the Sponsor:	Chief Investigator (CI)	Co-Investigator
Karen Jennings-Wilding Senior Clinical Research Governance Manager, University of Liverpool Clinical Directorate, The Quadrangle, Brownlow Hill, Liverpool, L3 5RB Tel no: 00 44 (0) 7717 863747 Email: Sponsor@liverpool.ac.uk	Dr Andreas Goebel Reader and Honorary Consultant in Pain Medicine, Clinical Sciences Centre, University Hospital Aintree, Liverpool, L8 7AL Tel no: +44(0) 151 529 5820 Email: Andreas.goebel@liv.ac.uk	Dr David Pang MB ChB FRCA Consultant in Pain Management Pain Management Centre, St Thomas' Hospital, Westminster Bridge Road, London, SE1 7EH Tel no: +44(0) 2071887188 Email: david.pang@gstt.nhs.uk

In cases where the CI is unavailable to respond to urgent queries the following individual/s will act as cover:

Medical Expert who will Advise on Protocol-Related Clinical Queries:	Medical Expert who will Evaluate SAE Reports:	Medical Expert who will Evaluate SAE Reports:
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Medical Expert who will Evaluate SAE Reports:	**<u>Add additional for any other experts i.e. for assessing SAEs in specific arms</u>**	
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Additional Contacts:

The contact details for the trial oversight committee members and participating centres are detailed in documents supplementary to the protocol and stored in the Trial Master File (TMF).

Table of Contents

2. Glossary

AE	Adverse Event
ALL	Dynamic Mechanical Allodynia
AR	Adverse Reaction
BPI	Brief Pain Inventory
CLCR	Creatinine Clearance
CI	Chief Investigator
CRF	Case Report Form
CRPS	Complex Regional Pain Syndrome
CTIMP	Clinical Trials of an Investigational Medicinal Product
CXR	Chest radiograph
EGFR	Estimated Glomerular Filtration Rate
EQ5D-5L	EuroQol
EU	European Union
EUDRACT	European Clinical Trials Database
GCP	Good Clinical Practice
GP	General Practitioner
HADS	Hospital Anxiety and Depression Scale
HRA	Health Research Authority
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IDSMC	Independent Data and Safety Monitoring Committee
IGRA	Interferon gamma release Assay
IMP	Investigational Medicinal Product
IL-1	Interleukin 1
ISF	Investigator Site File (part of the Trial Master File)
ISRCTN	International Standard Randomised Controlled Trials Number
LCTC	Liverpool Clinical Trials Centre
MA	Marketing Authorisation
MDT	Mechanical Detection Threshold
MHRA	Medicines and Healthcare Products Regulatory Agency
MPS	Mechanical Pain Sensitivity
MPT	Mechanical Pain Threshold
NHS	National Health Service
NIHR CRN	National Institute for Health Research Clinical Research Network
NIMP	Non-Investigational Medicinal Product
NRS	Numerical Rating Scale
PHQ-9	Patient Health Questionnaire 9
PI	Principal Investigator
PISC	Participant Information Sheet and Consent
PPT	Pain Pressure Threshold
PSF	Pharmacy Site File
QA	Quality Assurance
QC	Quality Control
QOL	Quality of Life

QST	Quantitative Sensory Testing
RA	Rheumatoid Arthritis
R&D	Research & Development
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RN	Research Nurse (Registered)
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TB	Tuberculosis
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
WOCBP	Woman of childbearing potential
WUR	Wind Up Ratio

3. Protocol Overview

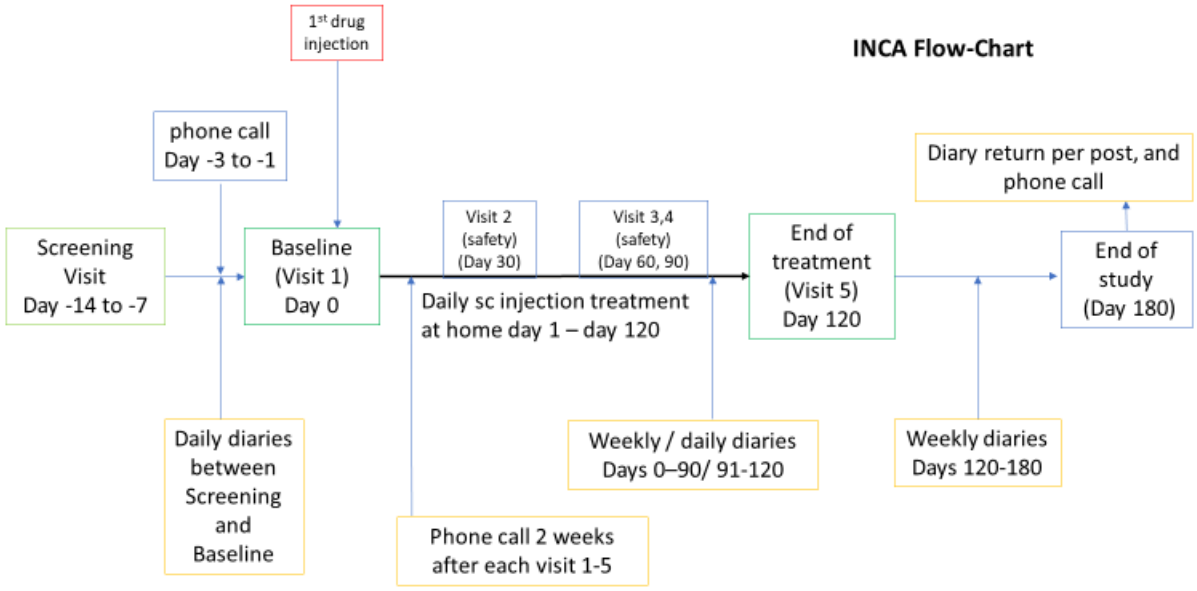
Full Title:	Interleukin-1 receptor antagonist treatment for refractory complex regional pain syndrome (CRPS)
Acronym:	INCA
Phase:	II
Target Population:	Adult Patients with moderate to severe CRPS that has been refractory to conventional management and a duration of 18 months to 15 years
Sample size:	30
Inclusion Criteria:	1. A diagnosis of CRPS I or II according to the Budapest research criteria at the time of the assessment for this study 2. First documented diagnosis of Budapest CRPS by a healthcare professional not less than 18 months and not longer than 15 years before the screening assessment. A valid documented diagnosis must either include the term 'Budapest CRPS' , or must include the term 'CRPS' **and** in addition documentation of the presence of signs and symptoms which allow making the Budapest diagnosis from the notes. 3. Pain intensity average 6 or greater on a 0-10-point numerical rating scale (NRS) over a minimum of seven consecutive daily entries prior to baseline (0 day) visit, with no single value below 5. 4. Completed a previous course of appropriate specialised physiotherapy 5. Poor response or intolerance to at least one anti-neuropathic pain medication such as tricyclic antidepressants or gabapentinoids. 6. If a woman of childbearing potential (WOCBP), to be willing to confirm the use of adequate birth control during the trial period unless pregnancy is impossible 7. Fertile male patients to be using contraception for the duration of therapy if sexually active with a female partner. 8. Age 18 years and over 9. Written and informed consent obtained from patient and agreement of patient to comply with the requirements of the study.

Exclusion Criteria:	1. Medical conditions that in the opinion of the study investigator would make it unsafe for participation or can adversely affect outcomes 2. Co-existing pain that in the view of the study doctor may make assessment of outcomes related to refractory moderate to severe CRPS unreliable 3. Ongoing relevant litigation where its conclusion is imminent during the course of the study 4. Medical Contraindications to anakinra such as moderate/severe or progressive renal impairment (CLCR < 60 ml/min or eGFR<60ml/min/1.73m2 or end stage renal disease, including dialysis), or hepatic impairment (defined as any value of transaminases, γ-glutamyl transpeptidase, or bilirubin greater than 2 times the upper normal limit) or hypersensitivity to anakinra or any of its excipients or to E.coli-derived proteins. 5. Previous use of anakinra 6. Current or recent (within 6 months) use of other immunosuppressants or biologics 7. Neutropenia defined as Absolute Neutrophil Count< 1.5 x 10^9/L 8. Requirement to receive a live vaccine during the trial duration. 9. Active or latent Tuberculosis infection 10. HIV, Hepatitis B or C carrier 11. Brittle asthma 12. Active malignancy or malignancy within 2 years 13. Ongoing alcohol or drug misuse at registration 14. Psychiatric or other mental health disorder which in the opinion of the study investigator may interfere with successful study participation 15. Commencing new therapy for refractory moderate to severe CRPS that may alter the outcome of the trial drug; this includes new pain management program treatment. Equally patients who have completed a pain management program within the past 3 months 16. Subject is pregnant or breastfeeding, inadequate birth control, or the possibility of pregnancy during the study. 17. Patients who have a spinal cord or dorsal root ganglion stimulator whose average pain is less than 6 out of 10 when the stimulator is on.

Study Centres and Distribution:	Two UK tertiary pain management centres with experience in managing refractory moderate to severe CRPS
Participant Study Duration:	**Duration of treatment:** 120 days per participant from baseline (0 day) registration **Duration of follow-up:** 180 days per participant from baseline (0 day) registration
Study Duration:	Trial recruitment and follow-up duration: 26 months and 2 weeks
IMP / Intervention:	**Intervention:** IMP: Anakinra Form: Solution for injection Dose: 100mg or 2mg/kg if body weight under 50kg Route: Subcutaneous injection
	Control: No control as study is a single arm study
Objectives:	
Primary:	To determine the safety and tolerability of anakinra in patients with refractory moderate to severe CRPS. This is defined as the proportion of patients with no serious or condition-specific adverse events (AEs). Pre-determined potential condition-specific AE's include persistent pain at injection site (greater than 1 week) of at least moderate intensity (5 or greater on a 0-10 NRS scale) and increase in CRPS-associated pain (>=2points NRS), ongoing for >1 month.
Secondary:	i) To identify any barriers to patient recruitment and retention, and ii) To obtain data that will in the future allow the design of a larger randomised controlled trial.

3.1 Schematic

Figure 1: INCA Summary Flowchart and Schedule of Assessments



4 Roles and Responsibilities

4.1 Sponsor

The University of Liverpool is legally responsible for the study. They will formally delegate specific Sponsoring roles to the CI and Clinical Trials Unit.

4.2 Funder

This study is funded by The Edelman Foundation.

Table 1: Funder contributions

Funder(s)	Role
Edelman Foundation	This funding source had no role in the design of this study and will not have any role during its execution, analyses, interpretation of the data, or decision to submit results.

4.3 Chief Investigator

Andreas Goebel is the CI for the trial and is responsible for overall design and conduct of the trial in collaboration with other members of the study team.

4.4 Principal Investigators

David Pang will be the Principal Investigator (PI) at the St Thomas' site and be responsible for identification, recruitment, data collection and completion of case report forms (CRFs), along with follow up of study participants and adherence to study protocol at that site. They will also be responsible for safety reporting and processing any applicable safety information.

4.5 Clinical Trials Unit

LCTC at the University of Liverpool in collaboration with the CI, will have overall management responsibility and will be responsible for trial management activities including (but not limited to) study planning, budget administration, TMF management, safety reporting, data management, randomisation, statistical analysis, participating site coordination and Investigational Medicinal Product (IMP) management.

Oversight Committees

The INCA trial is subject to oversight from the following committees:

4.6 Trial Management Group (TMG)

A Trial Management Group (TMG) will be formed comprising the CI, other lead investigators (clinical and non-clinical) and members of the LCTC. The TMG are responsible for monitoring all aspects of the progress and conduct of the trial and will be responsible for the day-to-day running and management of the trial. The TMG will meet at least monthly at setup stage and then reduce to quarterly throughout the year unless more frequent meetings are required.

4.7 Trial Steering Committee (TSC)

The Trial Steering Committee (TSC) will consist of an independent chairperson, 2 independent experts in the field of Pain Management, a biostatistician, and include the CI and observers. The role of the TSC is to provide overall supervision for the trial and provide advice through its independent Chairperson. The decision for the continuation of the trial lies with the TSC and as such they will meet throughout the trial (at least annually).

4.8 Independent Data and Safety Monitoring Committee (IDSMC)

The IDSMC will consist of an independent chairperson, plus 2 independent members who are experts in the field of pain management, and an independent biostatistician.

The IDSMC will be responsible for reviewing and assessing recruitment, interim monitoring of safety and effectiveness, trial conduct and external data. The IDSMC will first convene prior to the start of recruitment and will then define frequency of subsequent meetings (at least annually). Details of the progression guide and monitoring are provided in Section 11.

The IDSMC will then provide a recommendation to the TSC concerning the continuation of the study.

4.9 Protocol Contributors

Table 2 Protocol Contributors

Name	Affiliations	Contribution to protocol
Andreas Goebel	University of Liverpool	Protocol development and review
David Pang	Guys & St Thomas'	Protocol development and review
Kellie Platt	University of Liverpool	Protocol development and review
Simon Winn	University of Liverpool	Protocol development and review
Elaine Howarth	University of Liverpool	Statistical Input during development
Michaela Brown	University of Liverpool	Statistical Input during development
Rachael Cooper	University of Liverpool	Statistical Input during development
Dawn Greene	University of Liverpool	Protocol amendment and review
Tracy Moitt	University of Liverpool	Protocol amendment and review
Ruth Knight	University of Liverpool	Statistical Input and review
Helen Eccleson	University of Liverpool	Protocol amendment and review

5 INTRODUCTION

5.1 Background

Complex Regional Pain Syndrome (CRPS) is a condition that causes chronic refractory and debilitating neuropathic pain in a limb affected by trauma. This condition was initially described in soldiers who, despite recovering from wounds, developed unusual features of persistent pain, limb swelling and discolouration. In the majority of patients that suffer from trauma, the recovery is predictable and pain subsides after tissue healing. A small proportion of patients suffer with persistent pain despite this tissue healing, and some can go on to develop both ongoing pain and disordered function and autonomic features in the affected limb. This condition has been termed CRPS and it results in both chronic neuropathic pain and associated autonomic and inflammatory symptoms and signs. These features are disproportionate to the precipitating injury and in a small proportion of patients a history of injury cannot be recalled.

It remains an uncommon condition with an incidence of 20-26/100 000 but is poorly recognised by health professionals. The mean age affected is between 50 and 60 years old and female:male ratio is 3:1 approximately.

As the condition becomes chronic and refractory it is associated with functional impairment, psychological morbidity, loss of employment and an overall decreased quality of life (QoL). Unfortunately, as its pathophysiology is still unknown, many treatments are not effective. The mainstay of therapy is to reduce pain, allow physical and psychological rehabilitation and support with patient education. There are no treatments that target the underlying pathophysiology of this condition; all therapies ultimately aim to restore function and empower patients to manage their symptoms.

Once patients have exhausted conventional management strategies such as physiotherapy, pain education, interventional and pharmacological management and psychological rehabilitation there is no further medical input and they have to self-manage their symptoms. Although patients often get better, either spontaneously or with treatment, there remains a proportion of about 15% of patients that remain refractory and suffer from ongoing pain and disability. A very small number of patients with CRPS may benefit from neuromodulation but this still leaves many without any medical treatment options.

One hypothesis of how CRPS affects the limb is that of immune dysfunction. This has been studied by passive transfer of immunoglobulin G from patients with CRPS into rodents intraperitoneally. This transfer elicits unilateral hyperalgesia and autonomic signs in hind paw injured rodents and suggests that there may be an autoantibody process that is made pertinent by trauma. To test this further, application of Interleukin 1 (IL-1) has been studied; IL-1 knockout mice as well as mice treated early with anakinra (an IL-1 receptor antagonist) did not develop CRPS in the passive antibody transfer model, and the established CRP phenotype was reversable by later treatment. This suggests a pivotal role of IL-1 in the pathogenesis of CRPS and a possible target for clinical treatment.

5.2 Rationale

The exact pathophysiology of CRPS is still not fully understood. Many hypotheses have been suggested and this includes both physical as well as psychological aetiologies. This gap in our knowledge is a significant barrier to therapy as without a clear aetiology, it remains unknown how specific therapies will work in patients with refractory moderate to severe CRPS.

Clinical evidence of specific therapies such as steroids, bisphosphonates and immunoglobulins have shown negative results yet none have directly targeted specific components of the immune system that may be a principle cause of CRPS. Animal studies have shown that there is a significant immunological component to the pathophysiology of CRPS. IL-1 has been identified as a specific cytokine that plays an important role.
If IL-1 is a key component of the pathology of CRPS then targeting it should improve outcomes of patients with this condition.

Anakinra is an IL-1 receptor antagonist that competes with IL-1 beta for its receptor. It has found use in a number of autoimmune inflammatory conditions such as juvenile arthritis.
No studies have been performed on using anakinra in CRPS. We propose initially a small feasibility study in a small cohort of patients using anakinra to determine tolerability and safety in refractory moderate to severe CRPS, prior to a larger randomised controlled trial (RCT). Anakinra is well known in its use in rheumatoid arthritis (RA) and periodic fevers and has a good safety profile in these conditions.

5.2.1 **Drug dosage and duration of treatment**

Dosages

The dose of anakinra in the British National Formulary is 100mg daily by subcutaneous injection for RA and Stills disease. The dose for cryopyrin associated periodic syndromes is 1-2mg/kg if severe and up to a maximum of 8mg/kg. The dose of 100mg daily by subcutaneous injection is used in the most recent 3 out of the 5 large RCTs of anakinra in RA.

Other uses of anakinra include:

1. Familial Periodic Fever. A dose of 100mg daily by subcutaneous injection was used for 4 months in a RCT. Adverse event (AEs) were comparable in anakinra and placebo group.
2. Gout. 100mg daily by subcutaneous injection for 5 days. No serious adverse event (SAE) observed.
3. Pericarditis. Case reports using 100mg daily subcutaneously. Duration of treatment 9 months. Only mild adverse reactions (ARs) reported.
4. Adult onset Stills disease. 100mg daily subcutaneously for 24 weeks

Bresnihan 1998 [26] used three different anakinra doses, 30mg, 75mg and 150mg with the higher doses being more effective. Duration of drug administration was 24 weeks.

Cohen 2002 [27] used 0.1mg/kg, 0.4mg/kg and 2mg/kg daily subcutaneous anakinra doses.
More recent studies by Cohen 2004 [28], Fleischman 2003 [29] and Genovese 2004 [30] used 100mg daily subcutaneously.

Duration of drug administration was 6 months in the Fleischman 2003 [29] study, Cohen 2002 [28] was 12 weeks with an extension to 24 weeks and Genovese 2004 [30] and Cohen 2004 [28] followed up for 24 weeks.

Doses of anakinra between 50-150mg daily provided improved outcomes compared to lower doses. AEs did not differ between the high and lower doses.

The choice of dosage is based on CRPS being a chronic immune disorder and using a similar dose of anakinra to suppress immunity in conditions such as RA and stills disease.

Given that the dose of 100mg daily by subcutaneous injection is used by the majority of investigators using anakinra in the therapy of immune-related chronic disorders we chose this as an appropriate dosage for the therapy of CRPS. Higher doses could not be justified as CRPS does not share the same high levels of systemic immune activation seen in sepsis, covid-associated illness or severe Cryoporphyrin associated periodic syndromes.

Duration of anakinra

There is considerable variation in the duration of anakinra therapy in many of the indications above. CRPS is a chronic condition that can be present for many years. Many of the studies in RA used a duration of 12-24 weeks. Familial periodic fever was 4 months and gout was only for days as the natural history for acute attacks are very short.

4 months was chosen for anakinra in CRPS as we wanted to determine primarily safety and tolerability. Most AEs are seen at 4 weeks and can last 14-28 days. 4 months will allow for observation and follow up of adverse effects and to enable patients to observe the benefits of rehabilitation if anakinra has beneficial effects on pain and function.

5.3 Risk and Benefits

All potential risks and benefits will be discussed with each patient prior to entry into the trial. Details will be given to all participants on the participant information sheet.

5.3.1 Potential Risks

As Anakinra is currently used for treating autoimmune diseases it has a well-established side effect profile. There are not expected to be any specific side effects that relate to refractory moderate to severe CRPS with the exception of possible increases in pain,and new pain at the subcutaneous injection side. The latter is a relevant potential risk as CRPS is a post-traumatic condition and an injection constitues a very minor trauma; this risk will be carefully monitored. Injection sites will be rotated to minimise this risk. Of note, in the CRPS literature there are to our knowledge no reports about development of new CRPS at subcutaneous injection sites in patients with established refractory CRPS.

Anakinra can cause ARs such as:

1. Worsening of CRPS symptoms (presumed risk)
2. New CRPS symptoms at the IV injection site (presumed risk)
3. Nausea, vomiting, diarrhoea and abdominal pain (10%)
4. Headache (12%)
5. Joint pain (0-12%)
6. Flu like symptoms
7. Infection, bruising and swelling at the injection site

The most serious side effect include infections and neutropenia but these are rare. There is a risk of hypersensitivity at 0.1-1% but severe reactions are rare.

Currently with the Covid-19 pandemic there is a potential risk if participants are infected taking anakinra. These risks are not fully known and careful judgement must be made to balance the risk of potential infection with possible benefits. Of note, Anakinra is currently used in a number of clinical trials to treat the systemic immune response to Covid-19 infection. There is no contra-indication to the current vaccines against Covid-19 for patients on anakinra as these vaccines are not live.

Mitigation of risk will be done by increased follow up and surveillence compared with standard follow up with participants on Anakinra. While these ARs are known or specifically assumed side effects of anakinra, all serious and non-serious AEs will be reported (see section 13).

Investigators will be made aware of any changes in the Summary of Product Characteristics (SmPC) but the protocol will not need to be amended unless it directly affects the conduct of the study.

This trial is categorised Type B (somewhat higher than the risk of standard medical care) as per the risk-adapted approach to clinical trials adopted by the MHRA.

More detail regarding management of risks associated with this trial are detailed in a separate Risk Assessment maintained in the TMF.

5.3.2 Potential Benefits

The potential benefit of this intervention is improvement in pain and function in patients with refractory moderate to severe CRPS and reduction of the need for further medical input and visits to health

professionals. Overall, benefit is aimed at improving long term QoL. However, in this trial, even if participants experience such benefits they will not receive the drug after the end of the trial. They will be informed about this before consent.

5.4 Objectives

5.4.1 Primary Objective

To determine the safety and tolerability of anakinra in patients with refractory moderate to severe CRPS. This is defined as the proportion of patients with no serious or condition-specific AE's. Pre-determined potential condition-specific AE's include persistent pain at injection site (greater than 1 week) of at least moderate intensity (5 or greater on a 0-10 NRS scale) and increase in CRPS associated pain (>=2points NRS), ongoing for >1 month.

5.4.2 Secondary Objectives

The secondary objectives of the trial are:

i) to identify any barriers to patient recruitment and retention, and
ii) to obtain data that will in the future allow the design of a larger RCT.

6 STUDY DESIGN

INCA is designed as a single arm feasibility study of the use of Anakinra in an open-label cohort of patients with refractory moderate to severe CRPS. Two centres will be involved and Anakinra will be a fixed dose self-administered subcutaneously once daily for 120 days.

6.1 Blinding

This is an open label study; all researchers and participants know Anakinra is being administered to all participants.

6.2 Study Setting

Patients will be identified and recruited from two specialist pain management centres in the UK. Referrals to these centres are from both primary care and secondary care via GPs, allied health professionals and other pain management centres. Patients will also be recruited from National Health Service (NHS) CRPS registries and this will be done via written invitation. Follow up during the study will be in the two specialist pain management centres and once the study has completed, participants can have their follow up in secondary care or other NHS-affiliated community-based rehabilitation services as per standard care for these participants.

6.2.1 Selection of Participating Sites

Recruitment of patients will be from two centres- The Walton Centre Liverpool and Guy's and St Thomas' Hospital London which are specialist pain and CRPS clinics in secondary and tertiary care.

Criteria for the selection of centres are as follows:

1. Able to provide treatment and educate participants to self-administer Anakinra
2. Can offer comprehensive multidisciplinary care for managing refractory moderate to severe CRPS
3. PI as a pain management specialist
4. Provide laboratory facilities to process research blood samples
5. Clinical Equipoise
6. Local Research & Development (R&D) approval and ability to complete the research trial
7. Completion of Site Suitability Assessment and Delegation of authority and signature log to LCTC
8. Signed contract between site and sponsor

Both sites fulfilling the trial-specific criteria selected to be recruitment centres for the INCA trial will be opened to recruitment upon successful completion of all global (e.g. research ethics committee (REC) and MHRA) and study-specific conditions (e.g. site personnel training requirements) and once all necessary documents have been returned to the LCTC. Initiation of sites will be undertaken in compliance with LCTC internal processes. Conditions and documentation required will be detailed on a LCTC Green Light Checklist maintained in the TMF and must be fully completed prior to opening sites to recruitment.

6.2.2 Selection of Principal Investigators

PIs will be required to demonstrate equipoise, relevant experience and commitment during early stage feasibility assessment. All investigators will have the particular medical expertise necessary to conduct the study in accordance to the protocol and all regulatory and ethical requirements. Written agreement to conduct research as such will be obtained prior to site initiation.

A suitable co-investigator should be identified at each site to deputise in case of PI absence.

7 ELIGIBILITY CRITERIA

The INCA trial aims to recruit 30 patients based on sample size calculations described in Section 14.2. All patients must provide written, informed consent before any study procedures occur (see Section 10.2 for more information regarding the informed consent processes) and must meet all eligibility criteria as described below.

We anticipate that patients who have refractory moderate to severe CRPS will mainly be recruited from the two trial sites (tertiary care). All will have completed conventional treatments (i.e. physiotherapy and drug treatments, see below) for CRPS and some will have failed spinal cord stimulation.

7.1 Inclusion Criteria

Patients eligible for the trial must comply with all of the following at baseline:

1. A diagnosis of CRPS I or II according to the Budapest research criteria at the time of assessment for this study.
2. First documented diagnosis of Budapest CRPS by a healthcare professional not less than 18 months and not longer than 15 years before the screening assessment. A valid documented diagnosis must either include the term 'Budapest CRPS' , or must include the term 'CRPS' **and** in addition documentation of the presence of signs and symptoms which allow making the Budapest diagnosis from the notes.
3. Pain intensity average 6 or greater on a 0-10 point numerical rating scale (NRS) over a minimum of seven consecutive daily entries prior to baseline (0 day) visit, with no single value below 5.
4. Completed a previous course of appropriate specialised physiotherapy.
5. Poor response or intolerance to at least one anti-neuropathic pain medication such as tricyclic antidepressants or gabapentinoids.
6. If a woman of childbearing potential (WOCBP), to be willing to confirm the use of adequate birth control during the trial period unless pregnancy is impossible
7. Fertile male patients to be using contraception for the duration of therapy if sexually active with a female partner
8. Age 18 years and over.
9. Written and informed consent obtained from patient and agreement of patient to comply with the requirements of the study.

Please refer to section 7.4 for contraception and pregnancy testing in relation to Inclusion criteria 6 and 7

7.2 Exclusion Criteria

Any patient meeting any of the criteria listed below at baseline will be excluded from study participation:

1. Medical conditions that in the opinion of the study investigator would make it unsafe for participation or can adversely affect outcomes.
2. Co-existing pain that in the view of the study doctor may make assessment of outcomes related to refractory moderate to severe CRPS unreliable.
3. Ongoing relevant litigation where its conclusion is imminent during the course of the study.
4. Medical Contraindications to Anakinra such as moderate/severe or progressive renal impairment (CLCR < 60 ml/min or Estimated Glomerular Filtration Rate (eGFR)<60ml/min/1.73m^2 or end stage renal disease, including dialysis), or hepatic impairment (defined as any value of transaminases, γ-

glutamyl transpeptidase, or bilirubin greater than 2 times the upper normal limit) or hypersensitivity to anakinra or any of its excipients or to E.coli derived proteins.
5. Previous use of Anakinra.
6. Current or recent (within 6 months) use of other immunosuppressants or biologics.
7. Neutropenia defined as Absolute Neutrophil Count (< 1.5 x 10^9/l).
8. Requirement to receive a live vaccine during the trial duration.
9. Active or latent Tuberculosis (TB) infection.
10. HIV, Hepatitis B or C carrier.
11. Brittle asthma.
12. Active malignancy or malignancy within 2 years
13. Ongoing alcohol or drug misuse at registration.
14. Psychiatric or other mental health disorder which in the opinion of the study investigator may interfere with successful study participation.
15. Commencing new therapy for refractory moderate to severe CRPS that may alter the outcome of the trial drug; this includes new pain management program treatment. Equally patients who have completed a pain management program within the past 3 months.
16. Subject is pregnant or breastfeeding.
17. Patients who have a spinal cord or dorsal root ganglion stimulator whose average pain is less than 6 out of 10 when the stimulator is on.

7.3 Co-registration Guidelines

To avoid potentially confounding issues, ideally participants should not be recruited into other trials during their participation in INCA. Where recruitment into another, non-interventional trial is considered to be appropriate and without having any detrimental effect on the INCA trial this must first be discussed with the LCTC who will contact the CI (Dr Andreas Goebel).

Individuals who have participated in a research trial of other drug or blood products within 12 months preceding screening will be ineligible for the INCA trial.

7.4 Contraception and pregnancy testing

A WOCBP is defined as fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient and confirmation with more than one FSH measurement is required.

Pregnancy tests for eligibility purposes must be from serum or a highly sensitive urine test. Pregnancy test will be completed at screening, 30, 60, 90 and 120 days.

A man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy.

Birth Control Methods which may be considered highly effective include methods that can achieve a failure rate of less than 1% per year when used consistently and correctly:

1. Combined (Oestrogen and progesterone containing) hormonal contraception associated with inhibition of ovulation:

- Oral
- Intravaginal
- Transdermal

2. Progesterone-only hormonal contraception associated with inhibition of ovulation:

- Oral
- Injectable
- Implantable

3. Interuterine device (IUD)
4. Interuterine hormonal-releasing system (IUS)
5. Bilateral tubal occlusion
6. Vasectomised partner provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomised partner has received medical assessment of surgical success
7. Sexual abstinence-only if refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

8 TRIAL TREATMENT / INTERVENTIONS

8.1 Introduction

Anakinra is a biopharmaceutical drug that neutralises the biologic activity of interleukin-1α (IL-1α) and interleukin-1β (IL-1β) by competitively inhibiting their binding to interleukin-1 type I receptor (IL-1RI). Interleukin-1 (IL-1) is a pivotal pro-inflammatory cytokine mediating many cellular responses including those important in synovial inflammation.

Anakinra will be administered at a dose of 100mg subcutaneously to eligible patients who are 50kg or over in body weight, or at a dose of 2mg/kg subcutaneously to eligible patients who have body weight less than 50kg. The prescribed dose will be calculated and retained from baseline (0 day) to 120 days. No dose modifications will take place beyond the baseline (0 day) visit. Participants will be taught how to self-administer safely. The IMP (Anakinra) will be manufactured by Swedish Orphan Biovitrum Ltd in accordance with all applicable guidelines (see section 8.3).

As this is a novel use of Anakinra in CRPS the trial will be open label to determine tolerability and safety.

8.2 Treatment Name / Description

8.2.1 Anakinra

Brand name / Active ingredient:	Kineret / ANAKINRA
Formulation:	Liquid for injection in a 0.67ml pre-filled syringe. Clear, colourless-to-white solution for injection that may contain some product-related translucent-to-white amorphous particles
Manufacturer:	**Swedish Orphan Biovitrum Ltd**
Packaging, storage and stability:	Anakinra is supplied in a pre-filled syringe and must be stored at a temperature of 2ºC to 8ºC. It has a shelf-life of 3 years. It must be stored in its original container to protect it from light.
Supplier's name:	Local pharmacy stock
Regulatory Status:	Market Authorised

8.3 Manufacturing and Distribution

Anakinra will be sourced from usual NHS stock. It comes in a graduated pre-filled syringe containing 100mg of Anakinra in 0.67ml.

Packing and labelling will be completed in accordance with Good Manufacturing Practice (GMP) Annex 13 requirements and good clinical practice (GCP) by the pharmacy units at both Guy's and St Thomas' Hospital and The Walton Centre Liverpool.

8.4 Preparation, Dosage and Administration

Anakinra is used within the clinical doses used for autoimmune diseases as described in the SmPC.

Anakinra will be administered at a dose of 100mg subcutaneously to eligible patients who are 50kg or over in body weight, or at a dose of 2mg/kg subcutaneously to eligible patients who have body weight less than

50kg. The prescribed dose will be calculated and retained from baseline (0 day) to 120 days. No dose modifications will take place beyond the baseline (0 day) visit. Participants will be taught how to self-administer safely. The IMP (Anakinra) will be manufactured by Swedish Orphan Biovitrum Ltd in accordance with all applicable guidelines.

Please refer to section 5.2.1(Drug dose and duration of treatment) for the rationale of the dose (100mg) and treatment duration.

An authorised study doctor will prescribe Anakinra according to the protocol and the medication dispensed according to local pharmacy practice. Participants will be informed of potential side effects and AEs. They will be advised to contact the research team if they occur.

All documentation of prescribing will be maintained in the pharmacy site file which will be added to the investigator site file (ISF) at the end of the study. Study specific prescription will be submitted to the pharmacy prior to the participants start of anakinra administration.

8.4.1 DISPENSING AND DISTRIBUTION OF INVESTIGATIONAL MEDICINAL PRODUCT

Within each pharmacy the study drug will be stored in a secure area according to local pharmacy policies. Anakinra will be dispensed at each clinic visit in accordance with the pharmacy manual, with each patient being provided with sufficient Anakinra to inject this once a day as per protocol. As this is an open label study there is no requirement to blind participants and study investigators. Site staff will be responsible for communicating with their pharmacy in availability, supply, dispensing and ordering of Anakinra for all participants clinic visits.

8.4.2 ADMINISTRATION OF INVESTIGATIONAL MEDICINAL PRODUCT

Anakinra is self-administered subcutaneously via a pre-filled syringe and a maximum of 100mg is given once daily (body weight 50kg or over). In body weight is less than 50 kg, the same syringe will be dispensed and instructions will be given only to administer part of the dose in the syringes to 2mg/kg and the rest discarded. The prescribed dose will be calculated and retained from baseline (0 day) to 120 days. No dose modifications will take place beyond the baseline (0 day) visit. The study team will educate the participants on safe administration and disposal of sharps. A specific sharps bin will be provided and participants will be given instructions to return full bins and obtain replacements.

8.5 Treatment Modifications

After the participant has entered the trial, the clinician is free to give alternative treatment / intervention to that specified in the protocol, at any stage, if s/he feels it to be in the best interest of the participant. However, the reason for doing so should be recorded and the participant will remain within the trial for the purpose of follow-up and data analysis according to the treatment option to which they have been allocated. Similarly, the participant remains free to withdraw at any time from the protocol treatment and trial follow-up without giving reasons and without prejudicing further treatment, see section 10.9.

8.5.1 Dose adjustments

Anakinra is administered as a fixed dose 100mg subcutaneously once daily for participants whose body weight is 50kg or more, participants with a body weight of less than 50kg will administer 2mg/kg

subcutaneously once daily. The prescribed dose will be calculated and retained from baseline (0 day) to 120 days. No dose modifications will take place beyond the baseline (0 day) visit

8.5.2 **Allergic reactions**

Allergic reactions, including anaphylactic reactions and angioedema have been reported uncommonly. The majority of these reactions are maculopapular or urticarial rashes.

Anakinra should not be administered if the subject is known to be hypersensitive to Anakinra, its excipients or to E.coli derived proteins.

If a severe allergic reaction occurs, such as widespread rash, anaphylaxis, any respiratory distress or cardiovascular symptoms then administration of Anakinra should be discontinued and appropriate treatment initiated. An End of treatment form should be completed and the AE documented.

8.5.3 **Hepatic Events**

Anakinra should be used with caution in participants with severe hepatic impairment- this would be an exclusion criteria for trial participation. No dose adjustment is required for participants with moderate hepatic impairment.

In clinical studies transient elevations of liver enzymes have been seen. These elevations have not been associated with signs or symptoms of hepatocellular damage, except for one patient with Systemic Juvenile Inflammatory Arthritis that developed a serious hepatitis in connection with a cytomegalovirus infection.

During post-marketing use, hepatic events not affecting liver function, have been reported. The majority of patients have been treated for Still's disease or have had predisposing factors, e.g. a history of transaminase elevations. In addition, cases of non-infectious hepatitis, including occasional events of acute liver failure, have been reported in patients with Still's disease during Anakinra treatment.

8.5.4 **Renal Events**

No dose adjustment is needed for participants with mild renal impairment (Creatinine Clearance (CLCR) 60 to 89 ml/min or eGFR 60-89ml/min/1.73m^2). In patients with moderate/severe or progressive renal impairment (CLCR < 60 ml/min or eGFR <60ml/min/1.73m^2) or end stage renal disease, including dialysis, we would exclude from the trial as per the trial exclusion criteria.

8.5.5 **Serious Infections**

Anakinra treatment should be discontinued if a serious infection develops. Serious infection is defined as life-threatening, fatal, requiring admission to hospital or intravenous antibiotics or resulting in significant disability. Non-serious infection may result in continuation of Anakinra if, in the opinion of the investigator, the infection does not result in morbidity, and is unlikely to progress with continuing use of Anakinra.

Anakinra has been associated with an increased incidence of serious infections (1.8%) vs. placebo (0.7%) in RA patients. For a small number of patients with asthma, the incidence of serious infection was higher in Anakinra-treated patients (4.5%) vs. placebo-treated patients (0%), these infections were mainly related to the respiratory tract.

The safety and efficacy of Anakinra treatment in patients with chronic and serious infections have not been evaluated. Anakinra should be used cautiously in patients with a history of recurring infections or with underlying conditions which may predispose them to infections.

The safety of Anakinra in individuals with latent TB is unknown but there have been reports of TB in patients receiving several biological anti-inflammatory treatment regimens. Patients should be screened for latent TB prior to initiating Anakinra. The available medical guidelines should also be taken into account.

Other anti-rheumatic therapies have been associated with hepatitis B reactivation. Therefore, screening for viral hepatitis should be performed before starting therapy with Anakinra.

8.6 Accountability Procedures

Trial specific accountability logs will be maintained by the dispensing pharmacy:

- Master accountability logs will document receipt of supplies. Shipment records must be maintained by the dispensing pharmacy.
- Per patient accountability logs will document dispensing and returns. A record of individual prescriptions will be kept. There will be reconciliation between doses recorded as administered and doses returned.

8.7 Assessment of Compliance

Compliance will be assessed by direct observation and observation of returned sharps bins.

8.8 Concomitant Medications/Treatments and Specific Restrictions

Medications Not Permitted/ Precautions Required

1. Live attenuated vaccines: live vaccines should not be given concurrently with Anakinra.
2. Anakinra should not be used in conjunction with other immunomodulating biologics such as Enantercept.

Data on Concomitant Medication

Concomitant medication information should be collected on a specific CRF.

All concomitant drug therapies received will be recorded at screening, baseline (0 day) and follow up but study participants should not receive any other investigational drugs or agents for the duration of the trial.

Details of medication interactions can be found at https://www.medicines.org.uk/emc/product/559 (Kineret SmPC). Formal studies have not evaluated interactions between Anakinra and other medications. The main risk is increased risk of myelosuppression with other immunosuppressive medications and biologics.

8.9 Overdose

Overdose is defined as more than 100mg of Anakinra administered subcutaneously within a 16 hour period. The maximal dose should not be exceeded during the study and any overdose will be treated as an AE/UAE/SAE.

No dose-limiting toxicities were observed during clinical studies. In studies of sepsis, 1,015 patients received Kineret at doses up to 2 mg/kg/hour i.v. (~35 times the recommended dose in RA) over a 72-hour treatment period. The AE profile from these studies show no overall difference from that seen in the RA studies.

Overdose will be monitored by both clinical assessment in conjunction with measurement of prescribed doses. All overdoses will be recorded as a protocol deviation and standard processes regarding AEs made if necessary.

Specific information on reporting AEs can be found in Section 13 .

8.10 **Unblinding**

As this is not a RCT, unblinding does not apply.

9 OUTCOMES

Primary Outcome

The proportion of patients with no serious or condition-specific AE's. Pre-determined potential condition-specific AE's include persistent pain at injection site (greater than 1 week) of at least moderate intensity (5 or greater on a 0-10 NRS scale) and increase in CRPS associated pain (>=2points NRS), ongoing for >1 month.

Secondary Outcome(s)

To identify any barriers to patient recruitment and retention:

1. Monthly registration rate.
2. The proportion of patients completing the study - retention rate, and reasons for non-completion.

To obtain data that will enable a larger RCT to be designed in the future:

3. Change of pain intensity measured on a 0-10 point NRS from baseline (0 day) to 4 months/120 days after completion of Anakinra administration. Pain intensity at 120 days is defined for the purpose of this study a mean of the weekly scores and daily over the last month of drug administration. This is determined by calculating the results of the patient pain diaries.
4. CRPS severity score
5. Global Impression of change
6. Analgesic Medication use
7. EQ-5D 5L
8. Patient Health Questionnaire 9 (PHQ-9)
9. Brief Pain Inventory (BPI)
10. Hospital Anxiety and Depression Scale (HADS)
11. Skin sensitivity measured by mechanical quantitative sensory testing (QST)
12. Limb Volume (Figure of 8)
13. Work status

Table 3: Timepoints for objectives and outcome measurements

Objectives	Outcome Measures	Timepoint(s) of evaluation
To determine the safety/tolerability of Anakinra	Proportion of patients without SAEs	Baseline (0 day) -180 days
To identify barriers to recruitment and retention	Monthly registration rate	Baseline (0 day)
	Retention rate (proportion of patients completing study) and reasons for non-completion	Day 120/180
To obtain data that will enable a larger RCT to be designed in the future	Change of pain intensity measured on a 10-point NRS	Baseline (0 day) – day 120
	CRPS Severity Score	Baseline (0 day), 30, 60, 90, 120 days
	Global Impression of change (PGIC)	Day 120
	Change in Pain Interference measures: PHQ-9, BPI and HADS	Baseline (0 day), 30, 60, 90, 120 days
	EQ5D-5L	Baseline (0 day), 30, 60, 90, 120 and 180 days
	Skin sensitivity measured by Mechanical QST	Baseline (0 day) and day 120
	Limb volume (by figure of 8)	Screening visit, 60 day and 120 days
	Work status	Baseline (0 day) and day 120
	Analgesic Medication use	Baseline (0 day) and day 120

10 PARTICIPANT TIMELINES AND ASSESSMENTS

10.1 Participant Identification

Recruitment of patients will be from two centres; The Walton Centre and Guy's and St Thomas' Hospital, which run specialist pain and CRPS clinics in secondary/tertiary care.

Potential participants will be identified in the outpatient clinics after referral from both primary care and other secondary care services, or from patient registries, where patients have agreed/consented to be contacted. Potential participants identified from outpatient clinics will be offered a participant information sheet and asked to attend a screening visit. The screening visit should be organised by the site via telephone, email or letter.

Participant information sheets should be provided to patients at least 24 hours before screening visit and during this visit there will be opportunities to ask staff about the trial procedures (see section 10.2).

10.2 Informed Consent

Informed consent is a process initiated prior to an individual agreeing to participate in a trial and continues throughout the individual's participation. Written informed consent is required for all patients participating in LCTC coordinated trials. The process should involve discussion between the potential participant and an individual knowledgeable about the research, the presentation of written material (e.g. information leaflet or consent document), and the opportunity for potential participants to ask questions and have these satisfactorily answered. In obtaining and documenting consent, the research team should comply with applicable regulatory requirements and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. Informed consent should be re-affirmed throughout the trial and all discussions and consent should be documented appropriately. If a potential participant does not want to provide consent they do not have to give a reason.

Prospective Informed Consent Process

Potential subjects will be identified by the investigator and/or authorised site personnel during their outpatient appointment or via patient registries. Prior to entering the study, the PI, or qualified designee, will explain to each subject all aspects of the clinical investigation that are relevant to the subject's decision to participate throughout the clinical investigation including, but not limited to, the following: the purpose and nature of the study, study procedures, expected study duration, available alternative therapies, and the benefits and risks involved with study participation and the potential treatment. The PI, or qualified designee, shall avoid any coercion or undue improper influence on, or inducement of, the subject to participate and will not waive or appear to waive the subject's legal rights. The research staff will facilitate verbal discussions about the research and the consent process, as well as providing answers to any questions that arise.

Ample time will be provided to read and understand the patient information document and the opportunity to ask questions. This includes a detailed explanation of the study and makes clear that the rights and welfare of the participants will be protected

Subjects will be informed of their right to withdraw from the study at any time without prejudice; consent forms will use local non-technical language and be provided in a language understandable to the subject.

After verbal and written information has been provided, the individual seeking consent will ensure that the patient has fully understood all the information and will ask if they are happy to consent to participation in the trial.

Written informed consent will be sought from patients who will be approached by the study team and invited to consider participation into the screening and main trial. Subjects will be given a copy of informed consent form.

Where this is the case, written informed consent will be obtained by means of a dated patient's signature on the consent form. This will be countersigned and dated by the person who obtained informed consent i.e. the PI or other appropriately qualified member of the research team who has been delegated this responsibility. Prior to participation in the study, the subject will receive a copy of the signed and dated written informed consent and any other written information provided to the subject.

The original signed document will be retained in the trial site's ISF and copies will be made:

- One copy provided to the patient for their information,
- One copy transferred to the LCTC via encrypted email.
- One copy filed in the participant's medical records paper/electronic.

N.B. Details of the consent process (date, persons involved, version and type of information sheet and consent form used) will also be recorded directly into the participant's medical records.

Consent forms will be signed and stored in the ISF with a copy in the patient hospital notes. Specific consent will be obtained to allow their General Practitioner (GP) to be informed of their inclusion in the study.

Participants will have the right to refuse ongoing participation without giving reasons at any time during the study. Please see withdrawal section 10.9.

10.3 **Screening Visit**

A screening log of all patients who are approached about the study will be maintained, including patients who decline to attend the screening visit or are not deemed eligible for participation, as this will provide important information for monitoring purposes. The screening log will assign all potential participants with a unique site screening number, which will be made up of a 3-digit sequential number (XXX). This number should be written on all samples and study documentation used prior to registration.

Screening logs will contain information on consented and non-consented patients. The data for those who are non-consented is considered fully anonymous to all individuals outside of the patient's usual clinical care team. Sites will maintain their own trial register linking patients screening and/or randomisation numbers to their identifiers. Under no circumstances will this log be returned to the LCTC.

During the Screening visit the following assessments will be carried out:

- Complete Informed Consent Form
- Screening eligibility assessment
- Patient demographics
- Medical history and examination
- Review of Concomitant Medications
- CRPS History and limb examination
- Limb volume
- Vital signs (weight, height, Heart rate (HR) and Blood pressure (BP))
- Pain severity on a 0-10 (NRS)
- Pregnancy test from all female subjects of child-bearing potential
- Issue pain diary (up to two weeks daily diary: only seven days before visit is required)
- Full blood count and differential.
- Serum biochemistry- Sodium, potassium, urea and creatinine.
- Liver function tests- Bilirubin, ALT, AST, ALP, GGT.
- HIV, Hepatitis B and C screen unless a screen has been done in the 3 months prior to the screening visit
- TB screen as either a Tuberculin Skin Test or TB Interferon-Gamma Release Assay(IGRA) unless a TB screen of either method has been done in the 3 months prior to the screening visit
- Chest X-ray unless one has been done in the last 12 months

Informed consent must be in place before any other trial specific assessments are performed. A screening CRF should be completed but only returned for participants who are later registered in the trial.

A daily diary will be given to each participant to record pain intensity scores over seven consecutive days prior to their baseline (0 day) visit. This score is a self-measurement pain intensity NRS with 0 as no pain and 10 as the worst pain possible. A mean pain intensity of 6 on a 0-10 point NRS over the seven consecutive daily entries prior to their baseline (0 day) visit is required for eligibility. The pain intensity must not have been less than 5 on any single day. Participants will be encouraged to complete the diary on each day around the same time. They are advised to not complete the diary in retrospect. After screening, participants will be contacted by telephone once, between 1 and 3 days prior to the baseline visit to check pain diary scores.The implications of taking Anakinra abroad (e.g. possible increased travel insurance premiums etc) will be discussed with the participant. Patients will be advised that Anakinra may not be stored outside of the fridge for periods in excess of 12 hours, and that where it is stored outside of the fridge for periods of up to 12 hours, it should be stored at an appropriate temperature (between 2°C and 8°C) using a cool bag.

If participants are not eligible at any point they will not be rescreened, unless the reason for non-eligibility is short term and has been resolved in the opinion of the investigator. Participants who are found to be ineligible during the screening visit or during the telephone call to check diary scores will not need to attend for the baseline visit. The baseline visit should be arranged during the screening visit.

10.4 **Registration/Baseline visit (Day 0 ,visit 1)**

Eligibility can only be confirmed by CI or PI or their delegate . Eligibility assessment must not occur until fully informed consent is documented. Eligibility criteria are described in detail in Section 7.

Eligibility confirmation must be documented in the participant's medical notes and then on the trial's Eligibility CRF. Details must include at a minimum who confirmed full eligibility, when this was confirmed, and when the participant was formally entered into the trial.

Eligibility will be confirmed in two stages, i) from information obtained at the screening visit, ii) from the results of pain diaries completed between screening visit and registration visit, and results of screening blood tests, and TB screening where appropriate.

Baseline assessments should be completed as per the Schedule of Assessments (Section 10.7) in order to accurately complete the Baseline CRF and collect the necessary information for the trial analyses. This includes the following assessments:

- Vital signs
- Pain Intensity on a 0-10 NRS with 0 being no pain and 10 being the worst pain experienced, over the past 24hr.
- CRPS Severity score
- PHQ-9
- EQ-5D-5L
- HADS
- BPI
- Mechanical QST – this will be completed twice for the purposes of the sub study: once blindfolded and once non-blindfolded with the order decided at random (see section 10.4.1)
- Work status
- Medication use in opioid (Morphine) equivalents

10.4.1 **Sub study Randomisation**

During the baseline visit, participants will be randomised to inform the order in which the baseline mechanical QST assessment should be performed. Randomisation will be via a secure (24-hour) web-based randomisation system controlled centrally by the LCTC. A personal login username and password, provided

by the LCTC, will be required to access the randomisation system; designated research staff will be issued with their personal login and password upon completion of training in the use of the system.

When the system requirements are confirmed, a unique randomisation number will be displayed on a secure webpage along with the allocated sequence for the QST to be completed in. An automated email confirmation will be sent to the authorised randomiser. Note that the randomisation number will not be required as a participant identifier for the purposes of the trial as the randomisation relates to the sub study only.

Randomisation: web access https://ctrc.liv.ac.uk/Randomisation/INCA

If there are any problems with the randomisation systems contact the LCTC on 0151 795 7795 or via email on INCA@liverpool.ac.uk

(Note that the LCTC is open from 0900 – 1700, Monday – Friday, excluding public holidays and University of Liverpool closure days.)

10.5 Registration

Participants will be registered into the trial once:

a) Fully informed written consent has been obtained (and appropriately documented)
b) Eligibility criteria have been fulfilled (and eligibility confirmed)
c) baseline (0 day) assessments have been completed (at least seven days after the screening visit).

At this point participants will be assigned a registration number, made up of the letter R, the 3-digit site code and a 3-digit sequential number (RXXX-XXX). This number should be written on all samples and study documentation used from this point onwards.

10.6 Intervention

Upon registration into the research trial, participants will be self-taught to administer Anakinra on that day. Anakinra will be dispensed at baseline and at each clinic visit in accordance with the pharmacy manual, with each patient being provided with sufficient Anakinra to inject this once a day as per protocol. It is the responsibility of the PI or delegated research staff to inform the pharmacy department at their centre of impending registrations to ensure there is sufficient supply of the study drug.

10.7 **Schedule for Assessments and Follow-up**

All assessments and follow up are to be conducted in line with the Schedule of Assessments below:

Table 4: Schedule of Assessments:

			Visit 1	Telephone follow up 1	Visit 2	Telephone follow up 2	Visit 3	Telephone follow up 3	Visit 4	Telephone follow up 4	Visit 5	Telephone follow up 5	
	Screening	Pre-baseline Telephone visit	Baseline^	Baseline +2wks	Day 30*	Day 30 +2wks	Day 60*	Day 60 +2wks	Day 90*	Day 90 +2wks	Time Point Day 120*	Day 180#	Premature Discontinuation
Procedures													
Signed Consent Form	X												
Registration			X										
Assessment of Eligibility Criteria	X		X										
Review of Medical History (including demographics)	X												
Review of Concomitant Medications	X		X	X	X	X	X	X	X	X	X	X	X
Study Intervention (Daily after baseline to day 120)			X		X		X		X		X		
Clinical Assessment – Medical History and examination	X										X		X***
Clinical Assessment – CRPS History and Limb Examination	X										X		X***
Clinical Assessment – Vital signs, weight, height, HR and BP	X		X		X		X		X		X		X***
Clinical Assessment – Limb Volume	X						X				X		
Pregnancy Test if applicable (Urine or Blood beta HCG)**	X				X		X		X		X		
Chest Radiograph (CXR) and TB Check/testing†	X												

				Visit 1	Telephone follow up 1	Visit 2	Telephone follow up 2	Visit 3	Telephone follow up 3	Visit 4	Telephone follow up 4	Visit 5	Telephone follow up 5	
		Screening	Pre-baseline Telephone visit	Baseline^	Baseline +2wks	Day 30*	Day 30 +2wks	Day 60*	Day 60 +2wks	Day 90*	Day 90 +2wks	Time Point Day 120*	Day 180#	Premature Discontinuation
TB screening (IGRA) skin test†		X												
Issue pain diary and collection		X		X		X		X		X		X		
Numerical rating Score for CRPS Pain		X	X	X	X	X	X	X	X	X	X	X	X	X
CRPS Severity score				X		X		X		X		X		
EQ5D-5L				X		X		X		X		X	X	
PHQ-9				X		X		X		X		X		
HADS				X		X		X		X		X		
BPI				X		X		X		X		X		
Work Status				X								X		
QST-blind and unblinded (+)				X								X+		
Global Impression of Change												X		
Assessment of Adverse Events				X	X	X	X	X	X	X	X	X	X	X
Blood sample collection	Clinical Chemistry/ Hepatic Function	X				X		X		X		X		X
	Haematology	X				X		X		X		X		X
Serology	HIV/Hepatitis B and C‡	X												
Research Blood sample		X										X~		

Each Time point for follow up schedule can be +/- 3 days.

^Time between Screening and Baseline should be no more than 14 days.

* Face to face appointment

** Additional pregnancy tests may be conducted during the participation of the trial if there is any suspicion of being pregnant

*** Type of Clinical assessment will be only completed if at a visit. If completed by phone no clinical assessment will take place

~ May be taken at earlier timepoint if participant withdraws before day 120.

+ unblinded QST

Study Completion

†unless a TB screen of either method listed has been done in the 3 months prior to the screening visit

‡unless a screen has been done in the 3 months prior to the screening visit

All follow up visits will be scheduled from baseline (Day 0). Each participant will complete treatment administration from day 0 to day 120 and will be followed up for 180 days in total. During this time, scheduled follow ups will be conducted via both telephone as well as clinic visits. No face to face study visits are planned after 120 days.

Following registration each participant will be given a diary that they will fill in and record their pain intensity in accordance with the schedule:

- Weekly between day 0 to day 90
- Daily Between day 90 to day 120
- Weekly between day 120 to day 180

Clinic Follow-Up Visits:

Participants will need to attend clinics for follow-up at 30, 60, 90 and 120 days. These visits should be arranged at the baseline visit post registration. The following data should be collected and assessments/activities performed at all visits (unless specified differently below):

- Concomitant medication
- AEs
- Further Provision of Anakinra
- Collection of safety blood samples
- Collection of research blood samples (30ml, day 120 only)
- Clinical assessment and examinations including:
    - Pain assessment on NRS from their pain diaries
    - Limb Volume (days 60 and 120 only)
    - Vital signs: BP, HR, and weight

Telephone follow ups:

Research nurses (RNs) will telephone participants approximately 2 weeks (+/-3 days) after each clinic visit up to day 120 when the last drug dose is administered, and a final telephone follow up at day 180 at the end of the trial. Telephone appointments will be arranged and conducted by local research teams. The following information should be collected and recorded on the appropriate CRF:

- Concomitant medication
- AEs
- Pain assessment up to 120 days at the end of drug administration (NRS)
- EQ5D-5L questionnaire at day 180

Efficacy Assessments

This trial is not designed to determine efficacy, however data will be collected on outcomes that will be used to determine efficacy in a future definitive trial. Outcomes are detailed in section 9.

Safety Assessments

All AEs will be actively monitored from the time of consent, however, only those which are related to study procedures will be monitored between consent and the baseline visit. In addition, assessment of AEs will be made at each clinic visit (baseline (0 day) , 30, 60, 90, 120 day and all post-clinic telephone visits (last telephone visit will take place on day 180 by a delegated research staff).

Blood sampling and monitoring (not including research bloods) will be performed at screening, 30, 60, 90 and day 120.

AE reporting is detailed in section 13.

Quality of Life Assessments

QoL will be measured by the EuroQol EQ5D-5L (baseline (0 day), 30, 60, 90, 120 and 180 day).

Health Economic Assessments

No formal health economic assessment will be made but work status will be noted on the CRFs.

Special Assays or Procedures

QST is performed at baseline and day 120 (detailed in Appendix 3. Quantitative Sensory Testing).

10.8 Sampling

10.8.1 Safety Sample Collection (Clinical Chemistry, Hepatic function and Haematology)

Please see schedule above and the INCA laboratory manual.

10.8.2 Research Sample Collection

Samples for future research will only be collected from participants who provide written informed consent at screening and if registered onto trial a further sample will be collected at 120 day.

A 30ml blood sample (research) will be collected at screening and day 120 in 3 x 10ml Vacutainer Serum Separating tubes (SST). These samples will be collected at the same time as samples taken for monitoring safety bloods. However, if a participant decides to withdraw from study before day 120 and is willing, the day 120 blood sample may be collected at an earlier visit if consented.

Sample kits will be provided by the LCTC.

10.8.2.1 Sample Processing, Storage and Handling

Samples are to be processed on site as serum and stored at -20ºC before being transferred to the Rheumatology labs in the Clinical Sciences Centre Aintree, Liverpool (3rd floor Clinical Sciences Centre). A log of time between sampling and freezing will be recorded.

Serum samples from the St Thomas' site will be transferred to Clinical Sciences Centre Aintree, Liverpool at the end of the study and where needed also during the study. Transfer of samples will be co-ordinated by the LCTC who will arrange a courier.

Once transferred to Liverpool, samples will be stored at -80ºC at the University of Liverpool labs based in the Clinical Sciences Centre, Aintree University Hospital.

Custodianship

Research samples will be stored for up to 25 years for future analysis of immune mediators or antibodies relevant to CPRS. The custodian of the samples is Dr Andreas Goebel.

10.9 Intervention Discontinuation and Participant Discontinuation/Withdrawal

In consenting to the trial, participants agree to all trial activities including administration of trial intervention and treatment and follow-up assessments/visits and data collection. Every effort should be made to facilitate the completion of these for every recruited participant. If it is not possible to complete these activities (or it is deemed inappropriate) the reasons why should be documented. The following sub-sections describe the different levels of discontinuation/withdrawal.

Premature Discontinuation of Trial Intervention

Participants may discontinue treatment for reasons including, but not limited to:

- Patient-led i.e. request by the patient / legal representative / consultee
- Unacceptable toxicity (see Section 13 for AE reporting)
- Intercurrent illness preventing further treatment.
- CRPS symptom progression which requires discontinuation of therapy or results in inability to continue to comply with study procedures
- Pregnancy
- Death
- Clinician-led:
    - Any change in the participant's condition that justifies the discontinuation of treatment in the clinician's opinion.
    - Reasons of non-adherence or non-compliance with treatment or other trial procedures
    - Participant meets an exclusion criterion (either newly developed or not previously recognised)
    - Participant unable to receive Anakinra for >=7 days consecutively

Discontinuation from Anakinra does not mean discontinuation of the study altogether, and the remaining study procedures, follow up assessment/visits and data collection should be completed as indicated in the protocol unless the patient requests to withdraw from further follow up visits. Data to be collected at the time of discontinuation will include the following:

1. Reason for discontinuation (if available)
2. Any AEs
3. Pain intensity score (NRS)

If a study participant is discontinued from the study early, an End of treatment CRF will be completed describing the reason for discontinuation. In situations where treatment is withdrawn due to an AE, participants will be followed up until resolution of that AE or determination that the participant's condition is stable. All AEs will be followed up until 180 day.

In case of a Participant Withdrawal the participant will be assessed for AEs, if any, and medication use.

Participant Withdrawal from Follow Up

Participants are free to withdraw from follow up at any time without providing a reason, though a reason should be recorded if one is given. Those who wish to withdraw from further follow-up will have the data collected up to the point of that withdrawal included in the analyses. The participant will not contribute further data to the study unless this is required by law (e.g. safety events).

The LCTC should be notified of withdrawals from the study as soon as possible, a completed Withdrawal from Study CRF must be returned to the LCTC within 7 days.

In situations where study withdrawal is due to an AE, participants will be followed up until resolution of that AE or determination that the participant's condition is stable.

In case of premature discontinuation, the participant will be assessed for AEs, if any, and medication use.

Participant Transfer

If a patient moves from the area, every effort should be made for the patient to continue in the trial if they are happy to travel to site from their new location. If they are no longer able to continue with study visits (and therefore study treatment) every effort should be made by the site to follow up the patient as far as is possible. The trial provides financial support to participants of travel expenses of up to £20 per visit.

Loss to Follow-up

A participant will be considered lost to follow up if s/he fails to return for 2 scheduled visits and is not contactable by the site research team.

If a participant fails to attend/facilitate a required study visit the following actions must be taken:

- Site will attempt to contact the participant and reschedule the missed visit and advise the participant on the importance of maintaining the assigned visit schedule.
- Before a participant is deemed to be lost to follow up, site research staff will make every effort to regain contact with the participant (i.e. 3 telephone calls and, if necessary, a headed letter to last known address). These efforts should be recorded in the participants medical notes.
- If the participant continues to be unreachable they should be considered withdrawn from the study with a primary reason of lost to follow up and this should be recorded on the appropriate CRF.

10.10 End of Trial

This will be defined as the date on which data for all participants are frozen and data entry privileges are withdrawn from the trial database. The trial may be closed prematurely by the TSC, on the recommendation of the IDSMC.

Site and closure activities will be centrally coordinated and conducted in accordance with LCTC processes regardless of whether the trial closes as planned or prematurely. This includes activities such as:

- End of Trial notification to REC and competent authority e.g. MHRA.
- Trial-related materials reconciled and returned/disposed of as appropriate see section 8.
- All site data entered onto the study database, discrepancies raised and satisfactory responses received.
- Quality Control (QC) checks of the ISF, PSF and TMF as appropriate.

Study Discontinuation

The CI reserves the right to suspend or terminate the study, but intends to only exercise this right for valid scientific reasons or reasons related to the protection of subjects. The trial may be closed prematurely by the TSC based on recommendations of the IDSMC.

Possible reasons for study termination include:

- Insufficient registration to complete the study within the expected timeframe as per progression rules in section 11.
- Identification of unacceptable safety profile; suspicion of an unacceptable risk will result in a suspension, confirmation of an unacceptable risk will result in termination. See section 13.
- Product performance/product supply issues.
- Discontinuation of product.

In cases of study suspension/termination, medical care will continue to be provided to participants registered in the study (e.g. assessment for AEs, programming parameter changes to address safety concerns/participant discomfort). Participants will be notified by the investigator of suspension/termination due to unacceptable risk or of termination due to any other cause.

11 PROGRESSION CRITERIA

Monitoring for clinical trial progress will focus on recruitment and safety. This will be done by the IDSMC.

The following factors will be used to inform the decision to progress into the next stage of the trial :

1. **Recruitment**. Assessed 6 months from recruitment start. Initial recruitment rate of 0.5 participants each month per centre for the first 6 months from recruitment start.
2. **Safety**. Assessed 12 months from recruitment start (or later if it takes longer for 10 participants to be registered): For the first 10 registered participants, 3 or less reporting persistent pain (greater than 1 week) at injection site of at least moderate intensity (5 or greater on a 0-10 NRS scale) or substantial CRPS pain increase (>=2points NRS), ongoing for >1 month despite and from the time of pain-related treatment stop.
3. **Safety**. Assessed 12 months from recruitment start: Consider stopping if 30% or greater of study participants experiencing a serious adverse reaction (SAR).
4. **Recruitment and adherence**: At 12 months from recruitment start to have at least 12 participants registered and at least 50% of registered participants completing their active treatment.
5. **Futility**. After 12 participants have been recruited and completed 4 months treatment period, an average of no pain increase among completed participants (to visit 5/ 120 day) and at least one participant reporting at least 2 points of pain reduction on the NRS (rounded to the nearest whole number), both these criteria referring to the average pain recordings over the last two weeks before visit 5 / 120 day compared to baseline (0 day).

The IDSMC will use the above progression rules as a guide during regular monitoring with regards to trial progress and will provide a recommendation to the TSC concerning continuing the study. The above are not intended as strict stop/start criteria.

12 SUB-STUDIES

QST in this clinical trial is part of a standard of care when assessing patients with CRPS. One risk of performing the mechanical component of QST is the patients can observe the testing process and this visual aspect may bias the sensory profile results. The aim of this sub-study is to determine whether participant observation of the assessment leads to visual bias and alters the results of QST.

We will do this by performing the test at day 0 (Baseline) blindfolded to mask visual cues and non-blindfolded which is standard. Therefore, the QST will be performed twice on each participant at baseline with the order determined at random via a web-based randomisation system.

The aim is to compare the QST results (measured as a standardised z-score) between mechanical components measured with and without visual cues. The QST measurements will be explained and demonstrated by a trained member of the research team prior to measurement. The methodology of performing the QST is detailed in 22.3. Once the QST process has been explained, the measurement will be performed both blindfolded and non-blindfolded in an order determined at random.

The impact on the main study will be negligible as this is not an interventional measure and pain measures are unaffected by QST. A statistical plan will be detailed separately from the statistical analysis plan for the main study.

Both the Liverpool and London sites will take part in this sub-study.

13 SAFETY REPORTING

Safety reporting in clinical trials is a legal and ethical requirement and it is imperative that all applicable requirements detailed here are followed during the trial.

13.1 Terms and Definitions

Adverse Event (AE)
Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Adverse Reaction (AR)
Any untoward and unintended response to an IMP related to any dose administered.

Condition Specific Adverse Event
Persistent pain at injection site (greater than 1 week) of at least moderate intensity (5 or greater on a 0-10 NRS scale) and increase in CRPS associated pain(>=2points NRS), ongoing for >1 month.

Serious Adverse Event (SAE)
Any untoward medical occurrence or effect that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect.

Serious Adverse Reaction (SAR)
An AR which meets the definition of serious (see Section 13.2) is a SAR. A SAR event that has been assessed as 'expected' (see Section 13.5 Expectedness) according to the Reference Safety Information (RSI) (see below) will remain classified as a SAR only, however some SARs that are considered 'unexpected' will be further classified as a Suspected Unexpected Serious Adverse Reaction (SUSAR) (see below).

Suspected Unexpected Serious Adverse Reaction (SUSAR)
An AR that is classed in nature as serious and "unexpected" (i.e. not listed within the RSI approved for the trial by the MHRA and current at the time of onset of the SUSAR).

Reference Safety Information (RSI)
The information used for assessing whether an AR is expected (see section 13.5). This is contained in the SmPC for the product and must be approved for use by the MHRA. The RSI used to assess the expectedness of a SAR must be the current approved version at the time of onset of the SAR. The RSI for this trial is defined in section 13.5.1.

13.2 Assessment of Seriousness

The assessment of seriousness of safety events should be performed by an appropriately delegated, medically qualified member of the site research team.

An adverse event / reaction is assessed as serious if it:

- Results in death;

- Is life threatening (i.e. the investigator considers the event places the subject at immediate risk of death from the experience as it occurred (this does not include an adverse experience that, had it occurred in a more severe form, might have caused death));
- Requires hospitalisation or prolongation of existing hospitalisation (hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition, including elective procedures that have not worsened, do not constitute an SAE);
- Results in persistent or significant disability or incapacity (substantial disruption of one's ability to conduct normal life functions);
- Consists of a congenital anomaly or birth defect (in offspring of subjects, or their partners, taking the IMP regardless of time of diagnosis);
- Other important medical events (these may not result in death, be life-threatening, an overdose, a secondary malignancy or require hospitalisation, but may be considered an SAE/experience when, based upon appropriate medical judgment, they may jeopardise the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition).

13.3 Severity of Adverse Events

All AEs should be assessed for severity. The assignment of the severity/grading should be made by the investigator responsible for the care of the participant using the definitions in the table below:

Table 4: Severity Grading

Severity	Description
Mild	Does not interfere with routine activities.
Moderate	Interferes with routine activities.
Severe	Impossible to perform routine activities.
Life-Threatening	
Death	

N.B. A distinction is drawn between **serious** and **severe** AEs. Severity is a measure of intensity (see above) whereas seriousness is defined using the criteria in Section 13.2. Hence, a severe safety event need not necessarily be a "serious" safety event.

13.4 Assessment of "Causality" - Relationship to Trial Treatment/Intervention

The assignment of the causality should be made using the definitions in the table below:

Table 5: Definitions of Causality

Relationship	Description
Unrelated	There is no evidence of any causal relationship. N.B. An alternative cause for the AE should be given
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).
Possibly	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).

Probably	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Almost certainly	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

Events that are assessed as being possibly, probably or almost certainly related will be reported as having a reasonable possibility of being related, and events assessed as unrelated or unlikely will be reported as having no reasonable possibility of being related.

Assessment of causality should be made based on known safety profiles of IMP, or SmPC, or Investigator's Brochure (IB) and known risk profiles of other drugs in the same class. If any doubt about the causality exists the local investigator should inform the LCTC who will notify the CI. In the case of discrepant views on causality between the treating investigator and others, the opinion of the treating investigator will never be downgraded and the MHRA/REC will be informed of both points of view.

13.5 Assessment of "Expectedness"

The CI (or delegate) for the INCA trial is responsible for determining whether a safety event is expected or unexpected, however a Medical Reviewer will not assess their own patients, these patients will be assessed by an independent Medical Reviewer. There is no requirement for a reporting investigator to make an assessment of expectedness.

An event will be considered unexpected if it is not listed within the current and approved RSI (see section 13.5.1) for the study at the time of the event's onset. The nature, severity, or frequency of the event should be considered – if this is not consistent with that described for the type of event in the RSI the event should be assessed as unexpected.

13.5.1 Reference Safety Information / Information used to Assess Expectedness

The RSI for INCA is Kineret subcutaneous injection 100mg, derived from section 4.8 of the SmPC, available at https://www.medicines.org.uk/emc/product/559

13.6 Time Period for Active Monitoring of Safety Events

IMPORTANT: Any safety events occurring after the end of the below-described "active monitoring" period which meet the definition of serious (see section 13.2) and are recorded for this study (see section 13.1) must continue to be reported by sites to the LCTC in accordance with the timeframes and procedures described in section 13.12. The same processes established for SAEs within the active monitoring period should be followed for these events.

Active monitoring of safety events experienced by trial patients will be carried out from the time of trial consent. Between the point of consent and baseline (Day 0) only safety events which are related to trial procedures will be monitored. Thereafter all safety events will be monitored, beginning with the baseline visit (0 Day), then every 30 days at clinic visits, and at all telephone calls between clinic visits until the 120 day visit (end of treatment). Further safety events will be monitored at the end of the study on day 180 which is 60 days after the last dose of Anakinra.

Pregnant women will be followed up until a completed outcome of pregnancy (see Section 13.8 for more information on reporting pregnancy).

13.7 Notes on Safety Event Recording

The following events must be recorded for the purposes of the trial:

- An exacerbation of a pre-existing illness
- An increase in frequency or intensity of a pre-existing episodic event/condition

- A condition (even though it may have been present prior to the start of the trial) detected after trial drug administration
- Continuous persistent disease or symptoms present at baseline (0 day) that worsens following the administration of the study/trial treatment
- Laboratory abnormalities that require clinical intervention or further investigation (unless they are associated with an already reported clinical event).
- Abnormalities in physiological testing or physical examination that require further investigation or clinical intervention
- Injury or accidents
- Pregnancy (See section 13.8 for more details)
- Weight loss of ≥4% within 4 months

Do not record:

- Medical or surgical procedures - the condition which leads to the procedure is the AE
- Pre-existing disease or conditions present before treatment that do not worsen
- Situations where an untoward medical occurrence has occurred e.g. cosmetic elective surgery[1]
- Overdose of medication **without signs or symptoms***[2]
- The disease being treated or associated symptoms/signs unless more severe than expected for the participant's condition

*N.B. If overdose occurred **with** resulting signs and symptoms that meet the protocol criteria for AE/AR/SAE/SAR/SUSAR then they should be reported accordingly (see section 13.12 for more information) and the overdose highlighted to the LCTC team.

13.8 Reporting of Pregnancy

If pregnancy occurs during either the intervention or follow up period of the trial this must be notified to the LCTC using the appropriate CRF within 24 hours of the research team becoming aware. The pregnancy must be followed up by the site research team until childbirth and reported to LCTC.

Any pregnancies which result in a safety event assessed as "serious" (e.g. birth defect) must also be reported separately on the appropriate Safety Event CRFs in accordance with processes described in section 13. All pregnancies and outcomes reported to LCTC will be notified to the study Sponsor and monitored by trial oversight committees.

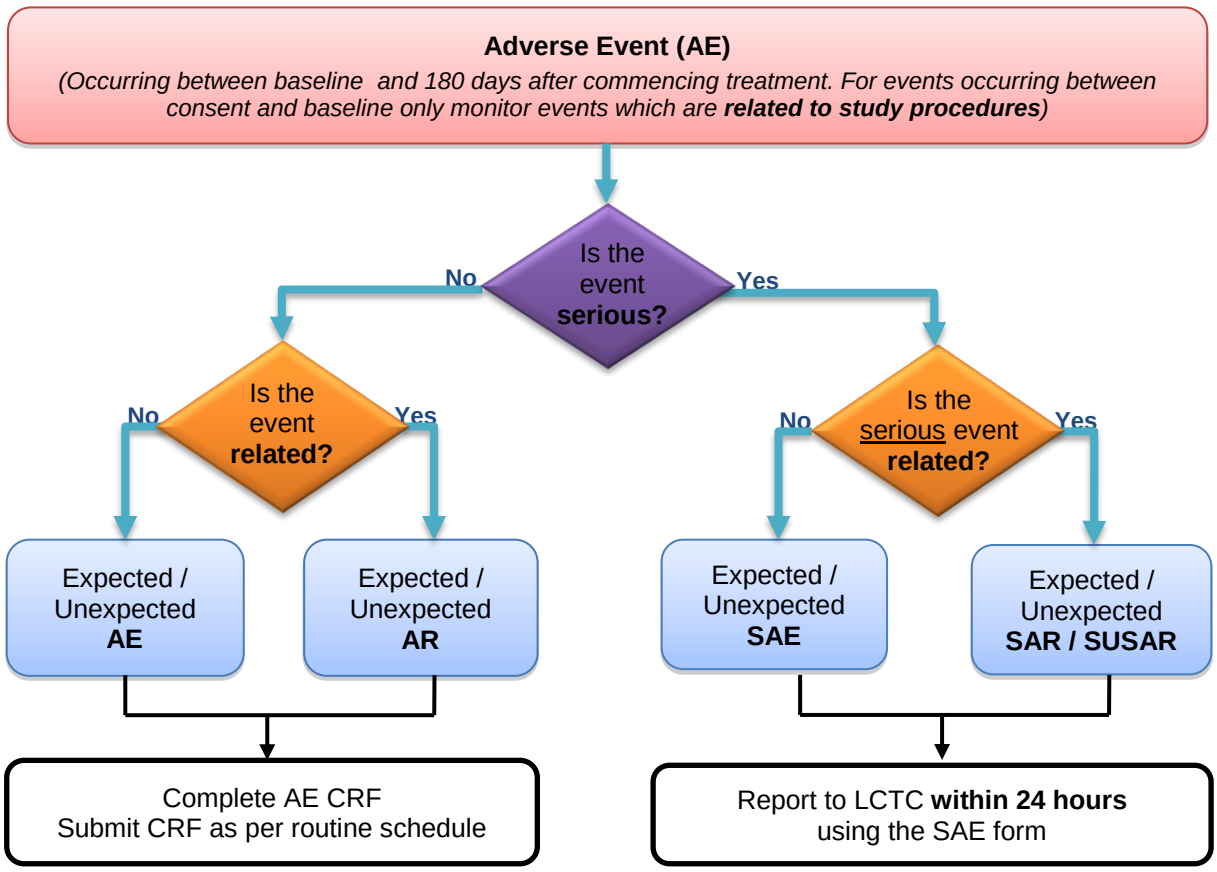
13.9 Notification of Deaths

If the research team become aware of the death of a participant (whether related to the trial or not) this should be notified to the LCTC using the appropriate CRF within 24 hours of becoming aware.

13.10 Reporting Procedures

All safety events which are recorded for the study should be reported following the procedures detailed below. The occurrence of a safety event may come to the attention of research staff during routine study visits, from the participant's notes, directly from the participant or by other means. Note that reporting procedures vary dependent on the nature of the incident (i.e. "serious" events are to be reported to LCTC in an expedited manner). Any questions concerning AE reporting should be directed to the LCTC in the first instance. A flowchart is given below to aid in determining reporting procedures for different types of AEs.

Figure 2: Flowchart for Site Reporting Requirements of Adverse Events



13.11 Reporting Safety Events to the LCTC

All safety events (whether or not assessed as serious / related / expected) should be recorded on an AE Form.

Safety events which are assessed as "serious" must **also** be recorded in more detail on SAE Forms; a single form is used for each individual event (i.e. a single diagnosis), though multiple symptoms can be recorded. Each SAE should have a corresponding record on the participant's AE form . Where additional information is received by site after initial submission to LCTC, this should be provided on a follow-up form within 5 days. SAE Forms collect data regarding the nature of event, date of onset, severity, corrective therapies given, outcome and causality; all serious events reported to LCTC will be reviewed by the CI or other Medical Reviewer, and assessed for causality and expectedness.

Follow-up After Adverse Events

All reportable AEs should be followed until satisfactory resolution or until the investigator responsible for the care of the participant deems the event to be chronic or the participant to be stable.

When reporting "serious" safety events the investigator responsible for the care of the participant should apply the following criteria to provide information relating to event outcomes:

- resolved
- resolved with sequelae (specifying with additional narrative)
- not resolved/ongoing
- ongoing at final follow-up
- fatal or unknown.

13.12 Investigator Reporting Responsibilities

The PI is responsible for ensuring that all safety events requiring recording on this study (see section 13) which the local research team becomes aware of are reported to LCTC. It is the responsibility of an appropriately medically qualified person as recorded on the Delegation Log to assess the seriousness and causality of events. When documenting any AEs, the correct medical terminology **must** be used.

All safety events must be recorded on an AE form and a copy of the form transferred to LCTC **within seven days of the site team becoming aware of the event**.

Safety events which meet the definition of "serious" must be reported in more detail to the LCTC on an SAE form and reported **immediately and in no circumstances later than 24 hours from becoming aware** unless the SAE is specified in the protocol as not requiring immediate reporting (see Section 13).

The SAE form should be completed by an appropriately delegated member of the research team; the assessments of seriousness and causality must be performed by an appropriately medically qualified person. Minimum reporting information must be provided in initial reports for all studies.

N.B. In the absence of a delegated medically qualified person the form should be completed and signed by an alternative member of the research site trial team and submitted to the LCTC. As soon as possible thereafter the responsible investigator should check the SAE form, make amendments as appropriate in line with GCP, sign and re-send to the LCTC. The initial report shall be followed by detailed follow-up reports as appropriate.

Safety events should be reported to the site R&D team in accordance with local policy.

Separate guidance are provided regarding appropriate completion of serious safety events.

REPORTING AN INITIAL OR FOLLOW-UP SAE
The investigator should ensure the actions below are completed for all reportable SAEs:

1) Research sites should telephone the appropriate trial team on telephone number **0151 795 7795** to advise that an SAE report will be submitted as soon as possible.
2) **The SAE form should be emailed securely to LCTCSafe@liverpool.ac.uk within 24 hours of becoming aware of the event. If email is not available please contact the trial team on 0151 795 7795.**
3) The responsible investigator must notify their R&D department of the event (as per standard local governance procedures).
4) The participant must be identified by trial number, age and initials **only**. The participant's name **should not** be used on any correspondence.
5) SAEs must be subsequently followed up in line with the processes below:
    - Follow up must continue until clinical recovery is complete and laboratory results have returned to normal, or until the event has stabilised (see Section 13). N.B. Follow-up may continue after completion of protocol treatment if necessary.
    - Follow-up information is noted on a new SAE form to be transferred securely to the LCTC as soon as more information becomes available
    - Tick the appropriate box on the new SAE form to identify the type of report; this is dependent on resolution status of the SAE e.g. follow-up / final.

Patient safety incidents that take place in the course of research should be reported to the National Reporting and Learning System (NRLS) by each participating NHS Trust in accordance with local reporting procedures. This also includes reporting any NIMPs.

13.13 LCTC Responsibilities

The trial Sponsor, (University of Liverpool) have delegated to LCTC the duty of onward reporting of safety events to REC, regulatory authorities and Sponsor. Standard Operating Procedures (SOPs) will be followed to ensure appropriate reporting as detailed below.

All “serious” safety events will be forwarded to the CI (or delegate) by LCTC within 24 hours of receiving the minimum information from site. The CI (or delegate) will review information provided by site and confirm the appropriate MedDRA code to be used for the event and assess ‘relationship’ and ‘expectedness’.

Safety events which are assessed as “serious”, “related” and “unexpected” will be expedited to the REC as applicable for clinical trials and applicable regulators, e.g. MHRA as a SUSAR within the following timeframes:

- SUSARs which are fatal or life-threatening – **as soon as possible and in any case no later than 7 days** after the LCTC is first aware of the event. If the initial report is incomplete, a complete report will be submitted within an additional 8 days.
- SUSARs that are not fatal or life-threatening – **within 15 days** of the LCTC first becoming aware of the event.

Additionally, SUSARs will be reported to the trial Sponsor and PIs of participating sites within the agreed timelines.

The LCTC will submit an Annual Safety Report to REC and a Development Safety Update Report to the MHRA on an annual basis.

The events below are considered for expedited reporting:

- An increase in the rate of occurrence or a qualitative change of an expected SAR, which is judged to be clinically important;
- Post-study SUSARs that occur after the participant has completed a clinical trial and are notified by the investigator to the Sponsor;
- New events related to the conduct of the trial or the development of the IMPs and likely to affect the safety of the participants, such as:
    - A SAE which could be associated with the trial procedures and which could modify the conduct of the trial;
    - A significant hazard to the participant population, such as lack of efficacy of an IMP used for the treatment of a life-threatening disease;
    - A major safety finding from a newly completed animal study (such as carcinogenicity).
    - Any anticipated end or temporary halt of a trial for safety reasons and conducted with the same IMP in another country by the same Sponsor;
    - Recommendations of the IDSMC, if any, where relevant for the safety of the participants.

The PIs at all institutions participating in the trial will be notified of any SUSARs within a reasonable timeline, and if appropriate.

Any concerns raised by the IDSMC or inconsistencies regarding safety reporting noted at a given site may prompt additional training at sites, with the potential for the LCTC to carry out site visits if there is suspicion of unreported AEs / ARs and SARs / SAEs in participant case notes. Additional training will also be provided if there are unacceptable delays in safety reporting timelines.

Urgent Safety Measures (USMs)

An urgent safety measure (USM) is a procedure to protect clinical trial participants from any immediate hazard to their health and safety but has not previously been defined by the protocol. It can be put in place prior to authorisation by the REC and the MHRA.

The LCTC will notify the MHRA and REC immediately and, in any event, within 3 days that such a measure has been taken and the reasons why it has been taken. The initial notification to the REC and MHRA will be by telephone (ideally within 24 hours) and a notice in writing will be sent within 3 days, setting out the reasons for the USM and the plan for further action. After discussion with the REC and MHRA, further action will be agreed, which may include submission of a substantial amendment, a temporary halt, or permanent termination of the trial.

Following notification, if a substantial amendment is required this must be submitted as soon as possible to the REC and ideally within two weeks to the MHRA. If the study is temporarily halted it may not recommence until authorised to do so by the REC and MHRA. If the study is permanently terminated before the date specified for its conclusion (in the original applications to REC and MHRA), the Sponsor should notify the REC and MHRA within 15 days of the date of termination by submitting the formal End of Trial Notification.

13.14 Contact Details and Out-of-hours Medical Cover

As Anakinra has a well-established safety profile, emergency and out-of-hours medical care will be in line with usual NHS arrangements and local standard practice; no special provision is required for INCA participants. All participants will be provided with a contact card and copy of the information sheet which includes information about their participation and contact details for the local research team who may be contacted if necessary. During office hours, the CI or delegate are able to provide medical advice in relation to participation using the contact details listed at the beginning of this document.

14 STATISTICAL CONSIDERATIONS

14.1 Introduction

All baseline, primary and secondary outcome measures will be reported using appropriate summary statistical measures. There are no formal hypotheses evaluated in this study.

14.2 Sample Size

A sample size of 30 has been estimated for this feasibility study. As this is a feasibility study, the sample size calculation can be difficult to determine.

Hertzog 2008 [38] recommends a sample size of between 20 and 40 patients for feasibility studies involving group comparisons. Hertzog suggests 30-40 patients per group will be required to yield confidence intervals whose lower limits can help define the range of plausible values for a subsequent power analysis.

Whitehead et al. 2016 [39] produced methods of calculating the optimal solution and approximate rules. For a main trial designed with 90% power and two-sided 5% significance, Whitehead et al. recommends a feasibility trial sample size per treatment arm of 75, 25, 15 and 10 for standardised effect sizes that are ≤0.1 (extra small), 0.2 (small), 0.5 (medium) and 0.8 (large) respectively.

The results of this feasibility study of 30 patients (single arm) will serve as data for sample size calculations for a further study. There are ethical and economic reasons for keeping this study population small, however the study results need to provide enough information to fulfil the specified primary and secondary endpoints.

With these reasons in mind and the recommendations of the two reference papers above, a sample size of 30 patients will be used for the INCA feasibility study.

The main outcome that will contribute to data for subsequent studies will be based on changes in pain intensity as measured by NRS (see Section 9). Feasibility data regarding the potential effects of Anakinra on pain intensity will be used to inform the sample size for the next stage of the study. The primary outcome of safety (throughout the study) and recruitment will be used to assess the rationale and feasibility of performing a larger RCT.

14.2.1 Feasibility of Sample Size

Between the two recruiting sites we expect a recruitment rate of one patient every month (across the two centres) for the first 6 months from commencing recruitment. In the second 12 months recruitment rate will be expected to be two patients monthly across both sites.

14.3 Interim Analyses

The trial will be assessed at regular intervals (at least annually) by the IDSMC. The IDSMC will be asked to review the conduct of the trial in terms of patient recruitment and safety/toxicity. Assessments of the primary endpoint shall be presented to the IDSMC in terms of the proportion of participants tolerating Anakinra and the safety of Anakinra in participants with refractory moderate to severe CRPS. The IDSMC will be asked to make a recommendation as to whether the study assessments presented at each meeting justify continuation of further patient recruitment and/or remaining follow-ups in accordance with the study protocol and guidelines on progression (as detailed in section 11 of the protocol).
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14.4 Analysis Plan

A full statistical analysis plan (SAP) will be written prior to the conduct of any statistical analysis of the cohort. The main features of the SAP are summarised below:

14.4.1 Patient Groups for Analysis

Full Analysis Set
In order to follow the Intention To Treat (ITT) principle this will consist of all eligible and registered participants at baseline (0 day) , excepting for: a) participants withdrawing consent between baseline (0 day) and starting therapy; b) participants withdrawn from the study after baseline (0 day) because of irregularities with the consent process; c) participants whose information determining ineligibility existed before registration but was not read until after registration.

Safety Set
All participants who received at least one dose of the trial treatment.

14.4.2 Assessment of Study Quality

Study quality will be summarised in terms of withdrawals / losses to follow-up, protocol deviations and extent of missing critical data.

14.4.3 Exposure to Treatment / Compliance

Exposure to treatment will be assessed by mean dose (mg) per participant. Dosing is once daily for a maximum of 120 days; the mean number of doses per participant over the treatment period (expressed as number of days treatment administered for) will be summarised.

Compliance of treatment will be captured by summarising the number of returned used syringes compared to non-used syringes.

14.4.4 Description of baseline (0 day) Patient Characteristics

Participant demographics and baseline (0 day) measures will be summarised appropriately for the cohort.

14.4.5 Missing data

As much information as possible will be collected about the reasons for missing outcome data. Final analyses are planned to be carried out on a complete case basis. Further details will be described in the statistical analysis plan.

14.4.6 Analysis of Outcomes

As this a feasibility phase II study, study outcomes are focused on safety/tolerability, recruitment and protocol /treatment adherence. Evaluations of further clinical/laboratory/QoL measures are also performed to provide useful information to inform further study designs and sample size calculations.

All outcomes will be summarised using appropriate summary measures.

15 DATA MANAGEMENT AND TRIAL MONITORING

For the INCA trial the responsibilities for Data Management and monitoring are delegated to the LCTC. Separate Data Management and Trial Monitoring Plans have been developed which provide detail regarding the internal processes that will be conducted at the LCTC throughout the trial. Justification for the level of monitoring is provided within those documents and the trial-specific risk assessment. All data will be managed as per local LCTC processes and in line with all relevant regulatory, ethical and legal obligations.

15.1 Source Documents

The CRFs will be considered the source documents for data only where no prior record exists and which is recorded directly in the bespoke CRF. An INCA source document checklist will be produced for each site to be kept in the ISF and provide detail of what constitutes INCA-specific source data.

Date(s) of informed consent processes (including date of provision of participant information, registration number and the fact that the participant is participating in a clinical trial (including possible treatment arms)) should be added to the participant's medical record chronologically.

15.2 Data Collection Methods

Participant CRF folders will be created by sites for local completion by members of the research team trained and delegated the duty. Study staff named at each site will enter data from source documents corresponding to a participant's visit onto the relevant CRF in the participant's folder. The CRF is the primary data collection instrument for the study so all data requested on the CRF **must** be recorded and all missing data must be explained. The wet ink CRF should be sent to LCTC and a copy of all CRFs should be retained at site. CRFs should also be emailed to LCTC via encrypted email. Any corrections prior to the submission of the wet ink CRF should be made in accordance with GCP. No amendments should be made to the copies of CRFs once the wet ink CRF has been returned to LCTC.

Questionnaires are a source document and **sites should photocopy them** in order to retain a copy at site before posting originals to LCTC. Questionnaires should also be emailed to LCTC via encrypted email.

15.3 Monitoring

Monitoring is conducted to ensure protection of participants participating in the trial and all aspects of the trial (procedures, laboratory, trial intervention administration and data collection) are of high quality and conducted in accordance with sponsor and regulatory requirements.

A detailed Trial Monitoring Plan will be developed and agreed by the TMG and CI to describe who will conduct the monitoring, at what frequency monitoring will be done, and what level of detail monitoring will be conducted. This will be dependent on the documented risk assessment of the trial which determines the level and type of monitoring required for specific hazards. All processes may be subject to monitoring, e.g. registration, consent, adherence to trial interventions, accuracy and timeliness of data collection etc.

Trial Oversight Committees related to the monitoring of the trial are detailed in Roles and Responsibilities see section 4.

Central Monitoring

There are a number of monitoring features in place at the LCTC to ensure reliability and validity of the trial data, to be detailed in the trial monitoring plan. Data will be entered into a validated database and during data processing there will be checks for missing or unusual values (range checks) and for consistency within participants over time. Other data checks relevant to patient rights and safety will also be regularly performed as per LCTC processes. Any suspect data will be returned to the site in the form of data queries. Data query forms will be produced at the LCTC from the trial database and sent either electronically or through the post

to a named individual (as listed on the site delegation log). Sites will respond the queries providing an explanation/resolution to the discrepancies and return the data query forms to the LCTC. The forms will then be filed along with the appropriate CRFs and the appropriate corrections made on the database.

Site monitoring visits may be 'triggered' in response to concerns regarding study conduct, participant recruitment, outlier data or other factors as appropriate.

Clinical Site Monitoring

In order to perform their role effectively, the trial coordinator (or monitor) and persons involved in Quality Assurance (QA) and Inspection may need direct access to primary data, e.g. patient medical records, laboratory reports, appointment books, etc. Since this affects the participant's confidentiality, this fact is included on the Participant Information Sheet and Consent (PISC). In agreeing to participate in this study, a PI grants permission to the Sponsor (or designee), and appropriate regulatory authorities to conduct on-site monitoring and/or auditing of all appropriate study documentation. The purposes of site monitoring visits include, but are not limited to:

- assessing compliance with the study protocol;
- discussing any emerging problems that may have been identified prior to the visit;
- checking CRF and query completion practices.

15.4 **Risk Assessment**

A risk assessment is completed in accordance with the LCTC SOP. Guidance from the MRC, Department of Health and MHRA on risk assessment on Clinical Trials of an IMPs (CTIMPs) suggest a three-level category of potential risks:

1. Type A- No higher than that of standard medical care
2. Type B- Somewhat higher than that of standard medical care
3. Type C- Markedly higher than that of standard medical care

Anakinra is a medicinal product that is licensed in the European Union (EU) for RA and for this trial it is for a new indication the risk assessment categorises the trial into type B- somewhat higher than that of normal medical care. As no clinical experience is noted with the use of Anakinra in CRPS, there is no justification to consider reclassification as type A. Clinical experience of Anakinra for inflammatory arthritis is overall positive regarding side effects and the main risk is of slightly increased incidence of infection and neutropenia in rare cases.

15.5 **Confidentiality**

This trial will collect personal data (e.g. participant names), including special category personal data (i.e. participant medical information) and this will be handled in accordance with all applicable data protection legislation. Data (including special category) will only be collected, used and stored if necessary for the trial (e.g. evidencing provision of consent, for data management and central monitoring, statistical analysis, regulatory reporting, etc.). At all times, this data will be handled confidentially and securely.

CRFs will be labelled with a unique trial registration number. Verification that appropriate informed consent is obtained will be enabled by the provision of copies of participant's signed informed consent forms being supplied to the LCTC by recruiting sites. This transfer of identifiable data is disclosed in the PISC.
N.B. Consent forms must be transferred separately to any other trial documentation to ensure the pseudonymisation of special category data is maintained.

Site-specific study-related information will be stored securely and confidentially at sites and all local relevant data protection policies will be adhered to.

The LCTC as part of The University of Liverpool will preserve the confidentiality of participants taking part in the study. The University of Liverpool is registered as a Data Controller with the Information Commissioners Office.

Breaches of data protection principles or regulations identified by LCTC will be notified promptly to the trial Sponsor and The University of Liverpool's Data Protection Officer and appropriate processes followed.

15.6 Quality Assurance and Control

To assure protocol compliance, ethical standards, regulatory compliance and data quality, as a minimum, the following will occur:

- The PI and other key staff from each centre will attend initiation training, which will incorporate elements of trial-specific training necessary to fulfil the requirements of the protocol.
- The TMG will determine the minimum key staff required to be recorded on the delegation log in order for the centre to be eligible to be initiated.
- The trial manager at the LCTC will verify appropriate approvals are in place prior to initiation of a centre and the relevant personnel have attended the trial specific training. A greenlight checklist will verify all approvals are in place prior to trial initiation at LCTC and the individual centre.
- The trial will be conducted in accordance with procedures identified in the protocol.
- The IDSMC and independent members of the TSC will provide independent oversight of the trial.
- The TMG will monitor screening, randomisation and consent rates between centres and compliance with the protocol.
- Data quality checks and monitoring procedures will be undertaken in line with the trial Data Management Plan.

15.7 Records Retention

The retention period for the INCA data and information is 25 years from the official End of Trial date (defined in section 10.10 above).

The PI at each investigational site must make arrangements to store the essential trial documents (as defined by ICH GCP guidelines) including the ISF, the applicable participant medical records and the PSF, for the full length of the trial's retention period, and will arrange for confidential destruction at the end of this period as instructed by the LCTC and Sponsor.

The PI is also responsible for archiving all relevant source documents so that the trial data can be compared against source data after completion of the trial (e.g. in case of inspection from authorities). They must ensure the continued storage of the documents, even if they, for example, leave the clinic/practice or retire before the end of required storage period. Delegation of responsibility for this must be documented in writing.

All other persons and organisations involved in the trial will be responsible for storing and archiving the parts of the TMF relevant to their delegated duties (e.g. laboratories).

The LCTC undertakes to archive as per their contractual requirements; documents will be archived in compliance with the principles of GCP. All electronic CRFs and trial data will be archived onto an appropriate media for long term accessible storage. Hard copies of data will be boxed and transferred to secure premises where unique reference numbers are applied to enable confidentiality, tracking and retrieval.

16 REGULATORY AND ETHICAL CONSIDERATIONS

16.1 Statement of Compliance

The study will be carried out in accordance with:

- The World Medical Association Declaration of Helsinki (1996)
- LCTC SOPs
- The Medicines for Human Use (Clinical Trials) Regulations 2004 (as amended)
- UK Policy Framework for Health and Social Care Research

16.2 Ethical Considerations

The trial will abide by the principles of the World Medical Association Declaration of Helsinki and has been designed to be as pragmatic as possible. The protocol has undergone ethical review by an independent REC and has received a favourable opinion

As Anakinra is used for a different indication it will pose some ethical concerns but as it is a well-established drug it is not anticipated there will be any major concerns. Participants will still have access to additional treatments as per routine care. Participation in this trial will not restrict access to additional treatments that would be deemed necessary.

16.3 Approvals

The trial will abide by the principles of the World Medical Association Declaration of Helsinki and has been designed to be as exploratory. The protocol will have undergone ethical review by an independent REC before initiation at the LCTC. Local independent R&D review at participating sites must also be obtained.

16.4 Protocol Deviation and Serious Breaches

Deviations from, breaches or violations of, or non-compliance to either the protocol, the conditions or principles of GCP, MHRA and REC requirements are handled based on their nature and severity.

Non-Serious breaches

Protocol deviations and other non-serious breaches of GCP etc. will be managed according to local site and LCTC procedures as appropriate. They will be reported to trial oversight committees.

Serious breaches

A breach of the protocol or GCP is ‘serious’ if it meets the definition of being “likely to affect to a significant degree the safety or physical or mental integrity of the trial participants, or the scientific value of the trial”. This assessment can only be determined by the Sponsor.

If any persons involved in the conduct of the trial become aware of a potential serious breach, they must immediately report this to the LCTC who will in turn notify the Sponsor. The Sponsor will assess the breach and determine if it meets the criteria of a ‘serious’ breach.

The Sponsor may seek advice from medical expert members of the TMG and/or of the independent oversight committees (IDSMC and TSC) in determining whether or not the breach is likely to affect to a significant degree the safety, physical or mental integrity of participants.

The Sponsor may seek advice from the Trial Statistician in determining whether or not the breach is likely to significantly affect the scientific value of the trial. However, the Sponsor retains responsibility for the assessment of whether or not a breach meets the definition of ‘serious’ and is subject to expedited reporting to MHRA and REC.

Breaches confirmed as ‘serious’ will be reported to MHRA and REC within 7 days by the LCTC on behalf of the University of Liverpool and notified to the TMG, IDSMC and TSC at their next meeting.
Any requests for additional information from the Sponsor, TMG, TSC, IDSMC, MHRA, or REC, will be promptly actioned by the relevant member(s) of the research team and open communication will be maintained to ensure appropriate corrective actions are taken and documented.

Incidents of protocol non-compliance will be recorded as protocol deviations, the incidence of which are monitored and reported to trial oversight committees.

17 INDEMNITY

The University of Liverpool holds insurance against claims from participants for harm caused by their participation in this clinical study. However, the treating hospital continues to have a duty of care to the participant and the Sponsor does not accept liability for any breach in the hospital's duty of care, or any negligence of the part of hospital employees. In these cases, clinical negligence indemnification will rest with the participating NHS Trust or Trusts under standard NHS arrangements.

18 PUBLICATION AND DISSEMINATION

18.1 Publication Policy

The results from different participating sites will be analysed together and published as soon as possible, maintaining participant confidentiality at all times. Individual clinicians must undertake not to submit any part of their individual data for publication without the prior consent of the TMG.

The TMG will form the basis of the writing committee and will advise on the nature of publications. The Uniform Requirements for Manuscripts Submitted to Biomedical Journals (http://www.icmje.org/) will be respected. All publications shall include a list of participants and if there are named authors these should include the trial's CI(s), Statistician(s) and Trial Manager(s) involved as a minimum. If there are no named authors (i.e. group authorship) then a writing committee will be identified that would usually include these people, at least. The ISRCTN allocated to this trial will be attached to any publications resulting from this trial and members of the TSC and IDSMC should be acknowledged.

Any publications arising from this research will be reviewed appropriately prior to publication.

Authorship

Contributors to all four of (i) the design, conduct, data analysis and interpretation, (ii) writing, (iii) manuscript approval and (iv) accountability for the integrity of the work will, depending on their contribution and journal requirements, be included by name at the manuscript head or listed at the end in a by-line which will also be named at the manuscript head.

18.2 Dissemination to Key Stakeholders

On completion of the research, a Final Trial Report will be prepared and submitted to the MHRA and REC. The results of INCA will be published regardless of the magnitude or direction of effect.

18.3 Data Sharing

At the end of the trial, after the primary results have been published, the anonymised individual participant data (IPD) and associated documentation (e.g. protocol, statistical analysis plan, annotated blank CRF) will be prepared in order to be shared with external researchers. All requests for access to the IPD will be reviewed by an internal committee at the LCTC and discussed with the CI in accordance with the LCTC policy on data sharing.

19 CHRONOLOGY OF PROTOCOL AMENDMENTS

List all amendments by number since the first final protocol was released. State where, how and why the protocol was changed. Include amendments to the protocol in the chronology and list in reverse chronological order (so the most recent amendment leads the section)

19.1 Version 8.0, 22/05/2024

Summary of Amendments from Protocol V7.0 to Protocol V7.1		
Protocol Section Number	**Protocol Section Title**	**Summary of Changes**
1	Protocol Approval	○ Lead Statistician signatory changed from Dr Ruth Knight to Michaela Brown.
3	Protocol Overview	○ Table section: Study Duration: amendment of duration from 26 months to 26 months and 2 weeks due to a 2-week “no-cost” extension to participant recruitment.

19.2 **Version 7.0, 12/02/2024**

Summary of Amendments from Protocol V6.0 to Protocol V7.0		
Protocol Section Number	**Protocol Section Title**	**Summary of Changes**
3	Protocol Overview	○ Table section: Study Duration: clarification of term and amendment of duration from 24 months to 26 months due to a 2-month extension to participant recruitment.
4	Roles and Responsibilities (4.2, 4.9)	○ Deletion of funding amount to avoid any further changes to this figure. ○ Update to table of protocol contributors with Ruth Knight, Helen Eccleson and Tracy Moitt.

19.3 **Version 6.0, 21/11/2023**

Summary of Amendments from Protocol V5.0 to Protocol V6.0		
Protocol Section Number	**Protocol Section Title**	**Summary of Changes**
10	Participant Timelines and Assessments	• Screening Visit: assessments: o HIV, Hepatitis B and C screen: addition of "unless a screen has been done in the 3 months prior to the screening visit" o TB screen as either a Tuberculin Skin Test or TB Interferon-Gamma Release Assay(IGRA): addition of "unless a TB screen of either method has been done in the 3 months prior to the screening visit" • Table 4 Schedule of Assessments: o footnote added to indicate that screening for HIV, Hepatitis B and C screen will only be done where these have not been screened for in the three months prior to the screening visit. o Footnote added to indicate that screening for TB will only be done where this has not been screened for in the three months prior to the screening visit.

19.4 **Version 5.0, 11/09/2023**

Summary of Amendments from Protocol V4.0 to Protocol V5.0		
Protocol Section Number	**Protocol Section Title**	**Summary of Changes**
na	Protocol Approval Authorisation	• Sponsor signatory: update to title from Miss to Mrs and to surname from Wilding to Jennings-Wilding
3	Protocol Overview	• Inclusion criteria: addition of lower limit of 18 months to disease duration, deleted in error in previous amendment • Inclusion criteria: rewording of response anti-neuropathic pain medication criterion • Exclusion criteria: clarification regarding renal impairment
7	Eligibility Criteria	• Inclusion criteria: addition of lower limit of 18 months to disease duration, deleted in error in previous amendment • Exclusion criteria: clarification regarding renal impairment
8	Trial Treatment / Interventions	• Deletion of IMP pack size details. • Specification of sufficient syringes to be supplied at every clinic visit
10	Participant Timelines and Assessments	• Screening Visit: o Addition of blood test for alkaline phosphatase (ALP) (currently tested as part of liver function tests but not listed separately in protocol) o Deletion of IMP pack size details. • Registration / Baseline visit: amended to indicate that eligibility may be confirmed by the CI‘s / PI ‘s delegate. • Sampling: o Safety Sample Collection: addition of ALP test (already being tested but not currently listed in the protocol. o Research Sample Collection: correction from 4 x 8.5ml serum separating tubes to 3 x 10 ml vacutainer serum separating tubes
13	Safety Reporting	• Reporting an initial or follow up SAE: contact number updated

19.5 **Version 4.0 (08/11/2022)**

Summary of Amendments from Protocol V3.0 to Protocol V4.0		
Protocol Section Number	**Protocol Section Title**	**Summary of Changes**
na	Protocol Approval Authorisation	• Addition of ISRCTN number • Lead Statistician signatory change to Dr Ruth Knight
na	Contact Details	• Addition of phone number for LCTC Trial Manager • Addition of medical experts with contact details
3	Protocol Overview	• Clarification regarding the diagnosis of CRPS • Increase in maximum disease duration from 10 years to 15 years • Planned recruitment start date, recruitment end date and follow up end date removed
4	Roles and Responsibilities	Addition of Dawn Greene to table of protocol contributors
7	Inclusion Criteria	• Increase in maximum disease duration from 10 years to 15 years • Clarification regarding the diagnosis of CRPS
8	Trial Treatment / Interventions	• Amendment and clarification of renal impairment exclusion criteria • Change of source website for SmPC to https://www.medicines.org.uk/emc/product/559
10	Participant Timelines and Assessments	• Screening visit: limb volume measurement added • Screening visit: inclusion of discussion with patients regarding the possible ramifications of travelling with the study drug • Screening visit: inclusion of advice to be provided by site staff regarding storing anakinra outside of the fridge (eg for travel purposes) • Baseline visit: limb volume measurement removed • Storage temperature of samples at site amended from -80°C to -20°C. • Participant transfer: clarification regarding follow-up by site
13	Safety Reporting	• Addition of event to be recorded as a safety event: weight loss of ≥4% over four months • Change in source website for SmPC to https://www.medicines.org.uk/emc/product/559 • Change in time period for active monitoring of safety events: only safety events related to study procedures will be actively monitored between consent and baseline. From baseline all safety events will be actively monitored.
15	Data Management and Trial Monitoring	• Additional instructions added regarding sending CRFs and questionnaires to LCTC: all CRFs and questionnaires to be sent to LCTC via encrypted email. • Confidentiality: deletion of paragraph stating LCTC would be responsible for questionnaire administration to trial participants.

19.6 **Version 3 (10/12/2021)**

Summary of Amendments from Protocol V2.0 to Protocol V3.0		
Protocol Section Number	**Protocol Section Title**	**Summary of Changes**
na	Protocol Approval Authorisation	• Sponsor signatory change to Miss Karen Wilding • Lead Statistician signatory change to Mrs Michaela Brown • Email change to Statisticians email address • Sponsor individual contact details amended
2	Glossary	• Addition of Hospital Anxiety and Depression Scale (HADS) • Addition of Participant Information Sheet and Consent (PISC) • Removal of a Catastrophisation Scale (PCS)
3	Protocol Overview	• Study Duration amended: Start date, recruitment end date and follow up date • Secondary Objectives were updated and secondary outcomes removed
5	Introduction	Secondary Objectives were updated and secondary outcomes removed
7	Eligibility Criteria	Inclusion criteria 7 separated in to two separate criteria (7 & 8)
9	Outcomes	• Wording of Objectives and outcomes have been amended for clarity. • Table timepoints updated and ‘analgesic medication use’ has been included
10	Participant timelines and assessments	• Participant identification amended • Screening updated: screening log • Screening CRF provided to LCTC only if a patient is registered • Sub study Randomisation included • Registration process clarified • Web based randomisation completed by site staff • Registration process paper based at site.
12	Sub-Study	Details of substudy evaluating the ordering of QST at baseline have been added.
14	Statistical Considerations	Feasibility of sample size: additional details of recruitment rate have been added for clarity.
14	Analysis of Outcomes	Primary and Secondary Outcomes removed from analysis of outcomes section (14.4.6) to avoid duplication of earlier sections.

19.7 **Version 2.0 (28/06/2021)**

Summary of Amendments from Protocol V1.0 to Protocol V2.0		
Protocol Section Number	**Protocol Section Title**	**Summary of Changes**
2	Glossary	Addition of Woman of childbearing potential (WOCBP)
3	Protocol Overview	Amendment to Inclusion criteria 6 and 7: clarification of childbearing potential and contraception Amendment to Exclusion criteria 4: added hypersensitivity
5	Introduction (5.2.1)	Rationale of doses proposed and treatment duration
7	Eligibility Criteria (7.1 and 7.2)	• Amendment to Inclusion criteria 6 and 7: clarification of childbearing potential and contraception • Amendment to Exclusion criteria 4: added hypersensitivity • Contraception and pregnancy testing
8	Trial Treatment/ Interventions (8.5)	Allergic reactions: hypersensitivity
10	Participant timelines and assessments (10.7)	• Schedule table: Addition of procedures at visit time points: Medical history (120 day), limb examination (120day), vital signs (30, 90 and premature discontinuation), pregnancy test (30, 60 and 120day) • Adverse events collected from screening
11	Progression rule	Consideration of stopping due to 30% serious adverse events at 12months.
12	Safety reporting	Reference to sections
19	References	Additional references: 20 – 37

19.8 **Version 1.0 (06/05/2021)**

Original Approved version

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21 DOCUMENTS SUPPLEMENTARY TO THE PROTOCOL

Documents referenced within the protocol are separately maintained and version controlled. Any of the supplementary documents subject to Competent Authority and / or Ethical review are submitted as separate version-controlled documents.

22 APPENDICES

22.1 Appendix 1. Research Diagnostic Criteria for Complex Regional Pain Syndrome

General definition of the syndrome:

Complex Regional Pain Syndrome describes an array of painful conditions that are characterized by a continuing (spontaneous and/or evoked) regional pain that is seemingly disproportionate in time or degree to the usual course of any known trauma or other lesion. The pain is regional (not in a specific nerve territory or dermatome) and usually has a distal predominance of abnormal sensory, motor, sudomotor, vasomotor, and/or trophic findings. The syndrome shows variable progression over time.

To make the clinical diagnosis, the following criteria must be met:

1. Continuing pain, which is disproportionate to any inciting event

2. Must report at least one symptom in all four following categories:

- Sensory: Reports of hyperesthesia and/or allodynia
- Vasomotor: Reports of temperature asymmetry and/or skin colour changes and/or skin colour asymmetry
- Sudomotor/Edema: Reports of edema and/or sweating changes and/or sweating asymmetry
- Motor/Trophic: Reports of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)

3. Must display at least one sign at time of evaluation in two or more of the following categories:

- Sensory: Evidence of hyperalgesia (to pinprick) and/or allodynia (to light touch and/or temperature sensation and/or deep somatic pressure and/or joint movement)
- Vasomotor: Evidence of temperature asymmetry (>1 °C) and/or skin colour changes and/or asymmetry
- Sudomotor/Edema: Evidence of edema and/or sweating changes and/or sweating asymmetry
- Motor/Trophic: Evidence of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)

4. There is no other diagnosis that better explains the signs and symptoms

22.2 **Appendix 2. Limb Volume Measurement-Figure of Eight Method**

This is performed using a flexible tape measure

Lower limb volume measurement

i. The zero of the tape measure kept on the mid-point between the articular projection of the anterior tibial tendon and the lateral malleolus.
ii. It is then wrapped medially to the distal side of the navicular tuberosity.
iii. Then it is wrapped across the instep to the proximal base of the 5th metatarsal.
iv. The tape is then drawn across the tibialis anterior tendon around the ankle joint to the medial malleolus.
v. At the medial malleolus, the tape is wrapped across the Achilles tendon and ending at the lateral malleolus back at the zero point.

Upper limb volume measurement

1. The zero point is set at the medial aspect of the wrist at the distal part of the ulna styloid process.
2. The tape is then wrapped across the ventral aspect of the wrist to the most distal point of the radial styloid.
3. The tape is then wrapped diagonally across the dorsum of the hand to the little finger metacarpal phalangeal joint.
4. Then it is wrapped across the ventral surface to the index finger metacarpophalangeal joint.
5. Finally, the tape is wrapped diagonally across the dorsum of the hand back to the starting point.

Esterson PS. Measurement of ankle joint swelling using a figure-of-eight. J Orthop Sports Phys Ther 1979;1:51-2.

22.3 **Appendix 3. Quantitative Sensory Testing**

All participants will be characterized by a limited QST Profile. These are focused on only the mechanical profiles and are performed according to the German Research Network on Neuropathic Pain (DFNS) in the affected body area. These tests are part of the baseline (0 day) profile and repeated at day 120.

1. Mechanical Detection Thresholds (MDT).
    a. This is measured using a standard set of modified Von Frey hairs which can exert forces between 0.25 and 512 mN. Contact time is over the painful limb and the contact area used is a rounded tip of 0.5mm diameter. Five threshold determinations were made and the final threshold measured as the geometric mean of these five done using ascending and descending intensities.
2. Mechanical Pain Thresholds (MPT)
    a. Seven weighted pinprick stimulators (*The PinPrick*™) which exerts forces between 8 and 512mN with a contact diameter of 0.25mm are used over the painful limb. Five threshold determinations were made and the final threshold measured as the geometric mean of these five done using ascending and descending intensities.
3. Mechanical Pain Sensitivity (MPS)

a. Using the same seven pinprick stimulators as 2, subjects were asked to give a pain rating for each stimulus on a 0-100 NRS (0 being no pain and 100 being the most intense pain imaginable). Five measures are used in a pseudorandom order intermingling with (4).

4. Dynamic Mechanical Allodynia (ALL)
    a. Three light tactile stimulators will be used over the painful limb:
        i. A cotton wisp exerting a force of approximately 3 mN,
        ii. A cotton wool tip fixed to an elastic strip exerting a force of approximately 100 mN,
        iii. A standardized brush exerting a force of 200-400 mN. One stroke is applied over 1-2cm across the skin over the painful limb. This is performed five times and a 0-100 NRS rating given as above.

    One stroke is applied over 1-2cm across the skin over the painful limb. This is performed five times in a pseudorandom order intermingling with (3) and a 0-100 NRS rating given as above.

5. Wind Up Ratio (WUR)
    a. A single pinprick stimulus is compared with that of a train of 10 pinprick stimuli of the same force repeated at a 1/s rate (256 mN when tested over hand and foot). The train of pinprick stimuli was given within a small area of 1 cm2 and the subject was asked to give a pain rating representing the pain at the end of the train using a NRS. Single pinprick stimuli were alternated with a train of 10 stimuli until both were done five times at five different skin sites within the same body region. The mean pain rating of trains divided by the mean pain rating to single stimuli was calculated as WUR. If 256 mN is perceived as being too painful (for the trains) or not reliably painful (for single stimuli) the testing force can be changed (lowest possible force: 32 mN, highest force: 512 mN) according to the subject's pain sensitivity. A rating range not exceeding 15/100 for single test stimuli will be most suitable.

6. Pain Pressure Threshold (PPT)
    This is performed by a conventional cylindrical shape pressure algometer (Wagner, USA) with a probe area of 1cm2. The probe is placed over the painful limb and the PPT will be assessed by steadily increasing the pressure by 50 kPa/s (equivalent to 0.5 kg/s) until the participant reports pain. Three ascending stimulus intensities will be measured.

The mechanical components of QST will be performed twice. Subjects will perform one set blindfolded and a second set without any visual restrictions. The order between these will be determined at random via a web-based randomisation process. QST will be performed by appropriately trained members of the research team.