Anakinra in the Treatment of Inflammation and Delirium after Orthopaedic Trauma and Repair (AnTIDOTe) Randomised Controlled Trial

Protocol version DRAFT 0.01

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This protocol has regard for the HRA guidance and order of content

This protocol has regard to ICH E9 statistical principles for clinical trials

0.1 FULL/LONG TITLE OF THE TRIAL

Anakinra in the treatment of inflammation and delirium in orthopaedic trauma and repair: a phase III, rater-blinded, bayesian-adaptive randomised placebo- controlled trial in people aged over 65 presenting with fractured neck of femur.

0.2 SHORT TRIAL TITLE / ACRONYM

Anakinra in the Treatment of Inflammation and Delirium after Orthopaedic Trauma and Repair (AnTIDOTe-RCT)

0.3 RESEARCH REFERENCE NUMBERS

Table 1: Research reference numbers

Organisation	Number
IRAS	3.18609×10^5
EUDRACT	
ClinicalTrials.gov	
ISCRTN	
University of Manchester	
KCL CTU	

0.4 TRIAL REGISTRY NUMBER AND DATE

0.5 PROTOCOL VERSION NUMBER AND DATE

v0.1 7th July 2022

0.6 SPONSOR

University of Manchester

0.7 FULL/LONG TITLE OF THE TRIAL

Anakinra in the treatment of inflammation and delirium in orthopaedic trauma and repair: a phase III, rater-blinded, bayesian-adaptive randomised placebo- controlled trial in people aged over 65 presenting with fractured neck of femur.

0.8 SHORT TRIAL TITLE / ACRONYM

0.9 PROTOCOL VERSION NUMBER AND DATE

0.10 RESEARCH REFERENCE NUMBERS

IRAS Number:

EudraCT Number:

ISRCTN Number / Clinical trials.gov Number:

0.11 SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, GCP guidelines, the Sponsor's (and any other relevant) SOPs, and other regulatory requirements as amended.

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

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

For and on behalf of the Trial Sponsor:

Signature: Date: ..07…./…08…/..2022… Name (please print): **Dr. Ross A. Dunne** Position: **Honorary Senior Lecturer**

Chief Investigator: Signature: [] Date: ……/……/…… Name: (please print):

(Optional)

Statistician: Signature:
Name: (please print): Position:

0.12 Key Trial Contacts

Table 2: Key Contacts

Chief Investigator	Dr. Ross A. Dunne
Trial Co-ordinator	Ms. Lynsey Hall
Sponsor	The University of Manchester
Join-sponsor(s) / co-sponsor(s)	Greater Manchester Mental Health NHS Foundation Trust
Funder(s)	National Institute for Health and Care research (NIHR)
Clinical Trials Unit	King's College London CTU
Key Protocol Contributors	Dr. Ross A. Dunne Prof. Leela Biant Prof. Colm Cunningham Prof. Stuart Allan Prof. David Brough Prof. Alasdair MacLullich
Statistician	TBD
Trials Pharmacist	Beatriz Duran
Committees	Data Monitoring and Ethics Section 1.1.2 Trial Steering Committee Section 1.1.1

0.13 LIST OF ABBREVIATIONS

AE	Adverse Event
AR	Adverse Reaction
CA	Competent Authority
CI	Chief Investigator
CRF	Case Report Form
CRO	Contract Research Organisation
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of Investigational Medicinal Product
CTU	Clinical Trials Unit
DMC	Data Monitoring Committee
DSUR	Development Safety Update Report
EC	European Commission
EMEA	European Medicines Agency
EU	European Union
EUCTD	European Clinical Trials Directive
EudraCT	European Clinical Trials Database
EudraVIGILANCE	European database for Pharmacovigilance

GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use.
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
ISF	Investigator Site File (This forms part of the TMF)
ISRCTN	International Standard Randomised Controlled Trials Number
MA	Marketing Authorisation
MHRA	Medicines and Healthcare products Regulatory Agency
MS	Member State
NHS R&D	National Health Service Research & Development
NIMP	Non-Investigational Medicinal Product
PI	Principal Investigator
PIC	Participant Identification Centre
PIS	Participant Information Sheet
QA	Quality Assurance
QC	Quality Control
QP	Qualified Person
RCT	Randomised Control Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
SSI	Site Specific Information
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee

0.14 TRIAL SUMMARY

Table 4: Trial Summary

Trial Title	
Internal Ref. no. (or short title)	AmTIDOTe
Clinical Phase	IIa
Trial Design	Randomised Controlled Rater Blind
Planned Sample Size	n=
Treatment Duration	72 hours post surgical repair
Followup Duration	One followup at 30 days
	Objectives
Primary	To compare the efficacy of Anakinra with placebo in the treatment and prevention of delirium in participants over 65 undergoing surgical repair of fractured neck of femur
Secondary	To compare the efficacy of Anakinra with placebo in the time to recovery (first stand) in participants over 65 undergoing surgical repair of fractured neck of femur
Exploratory	To compare the efficacy of Anakinra with placebo in the time to medical fitness for discharge in participants over 65 undergoing surgical repair of fractured neck of femur
	Outcomes
Primary	Confusion Assessment Method, Confusion Assessment Method Severity Observational Scale of Level of Arousal
Secondary	Time to stand Time to medical fitness for discharge
Investigational Medicinal Products	Anakinra
Formulation, Dose, Route of Administration	100mg Subcutaneous once daily until 72 hours post surgical repair of fractured neck of femur

0.15 ROLE OF TRIAL SPONSOR AND FUNDER

The sponsor has had no role in the design of the protocol or trial. The sponsor maintains responsibility for trial conduct, indemnity, data security and oversight. The sponsor will ensure

provision is made for insurance or indemnity to cover liabilities which may arise in relation to the design, management and conduct of the clinical trial. The sponsor will provide investigator(s) with the necessary information to conduct the clinical trial, ensure proper monitoring of the clinical study, ensure all necessary ethic review(s) and approval(s) are obtained. The sponsor will ensure that any reviewing ethics board and regulatory agencies are promptly informed of any significant new information (for example, important findings that affect product safety). The sponsor will ensure compliance with labelling, reporting and record-keeping requirements. The sponsor will ensure that the clinical study is conducted in accordance with Good Clinical Practice (GCP) and the Declaration of Helsinki. The sponsor will ensure that roles and responsibilities of the parties involved in the research and any delegation by the sponsor of its tasks are agreed and documented. The sponsor will ensure appropriate arrangements are made for making information about the research publicly available before it starts (unless a deferral is agreed by or on behalf of the research ethics committee); agreeing appropriate arrangements for making data and tissue accessible, with adequate consent and privacy safeguards, in a timely manner after it has finished; and ensuring arrangements for information about the findings of the research to be made available, including, where appropriate, to participants (For educational research, registration, accessibility of data and tissues, and dissemination may be limited to institutional arrangements). The sponsor will ensure that, where expected or required, the research has approval from a research ethics committee (Whether outright or following a provisional opinion, resubmission or appeal) and any other relevant approval bodies before it begins. The sponsor will verify that regulatory and practical arrangements are in place, before permitting the research to begin in a safe and timely manner. The sponsor will ensure adequate arrangements for finance and management of the research project, including its competent risk management and data management.

1 ROLES AND RESPONSIBILITIES OF TRIAL MANAGEMENT COMMITEES/GROUPS & INDIVIDUALS

1.1 Trial Management Committees

1.1.1 Trial Steering Committee

The Trial Steering Committee (TSC) will be of majority independent representation including participation by one or more lay persons, preferably with lived experience of delirium or caring for someone with delirium.

1.1.2 Data Monitoring and Ethics Committee

The Data Monitoring and Ethics Committee will be of independent representation where the committee members are completely uninvolved in the running of the trial and who cannot be unfairly influenced (either directly or indirectly) by people, or institutions, involved in the trial. At a minimum we will have one independent statistician, one lay member, one expert clinician (Chair)

1.1.3 Trial Management Group

The Trial Management Group (TMG) will consist of the Scientific Advisory Committee, members of the Clinical Research Team, the Clinical Trials Unit (CTU) Team and

1.2 Chief Investigator

The Chief Investigator (CI) will be the overall lead researcher for a research project. The chief investigator is responsible for the overall conduct of the trial, including:

a) satisfying themselves that the research proposal or protocol takes into account any relevant systematic reviews, other research evidence and research in progress, that it makes effective use of patient, service user and public involvement where appropriate and that it is scientifically sound, safe, ethical, legal and feasible and remains so for the duration of the research, taking account of developments while the research is ongoing;
b) satisfying themselves that the research proposal or protocol has been submitted for appropriate independent expert ('peer') review (For educational research, the chief investigator will be a supervisor who may provide an appropriate level of review) and revised in light of that review;

c) satisfying themselves that, if expected or required, the proposal has been submitted for review by and obtained approval from a research ethics committee and any other relevant approval bodies; satisfying themselves (For multi-site projects, this may be delegated to the principal investigator at each research site) that everyone involved in the conduct of the research is qualified by education, training (Training should be appropriate and proportionate to the type of research undertaken, and should cover the responsibilities of researchers set out in relevant legislation and standards – HRA planning and improving research page)
d) and experience, or otherwise competent, to discharge their roles in the project;
e) satisfying themselves that the information given to potential participants is in a suitable format and is clear and relevant to their participation in the research and, where consent is required, to their decision-making about taking part in the research – HRA decision tool.
f) adhering to the agreed arrangements (paragraph 8.10) for making information about the research publicly available before it starts (unless a deferral is agreed by or on behalf of the research ethics committee);
g) adhering to the agreed arrangements (paragraph 8.11) for making data and tissue accessible, with adequate consent and privacy safeguards, in a timely manner after the research has finished (Funders or others may set expectations about making data and tissue available);
h) starting the research only once the sponsor has confirmed that everything is ready for it to begin;
i) adhering to the agreed procedures and arrangements for reporting (e.g. progress reports, safety reports) and for monitoring the research, including its conduct, the participants' safety and well-being and the ongoing suitability of the approved proposal or protocol in light of adverse events or other developments; and
j) adhering to the agreed arrangements for making information about the findings of the research available, including, where appropriate to participants.

1.3 Protocol contributors

1.3.1 Scientific advisors

The idea for the use of Anakinra in preventing and treating delirium emerged from conversations between Prof. Colm Cunningham and Prof. Stuart Allan during and after an invited lecture at the Geoffrey Jefferson Brain Research Centre (GJBRC) at the University of Manchester. As Anakinra had been shown during the COVID19 pandemic to reduce the 'cytokine storm' associated with infection with the SARS-Cov-19 virus, th e rationale of extending use to delirium, where IL-1 production has been demonstrated in animals and humans to drive inflammatory responses and altered mentation, seemed promising. The GJBRC was created in 2021 to bring basic and clinical scientists together for the rapid translation of scientific findings into life-changing therapies for major health problems.

Prof. Colm Cunningham is a globally recognised leader in the basic science of neuroinflammation and cognition. His laboratory at the Trinity College Institute of Neuroscience (TCIN) in Dublin is one of the world's leading centres for such research. He has been the recipient of numerous awards and fellowships.

Prof. Stuart Allan leads a renowned neuroinflammation laboratory in the University of Manchester, where his groups is focused on the neuroimmunology of cerebral ischaemia. Working closely with stroke clinician-scientists and researchers at the GJBRC, the team are working on the reduction of post-stroke inflammation leading to dementia.

Prof. David Brough leads a renowned neuroinflammation laboratory in the University of Manchester, where his groups is focused on the molecular immunology of the inflammatory cascade and novel target and drug development. His team work closely with clinician-scientists at the GJBRC as well as colleagues in Oxford and further afield.

1.3.2 Clinical Researchers

Prof. Leela Biant is the Academic head of department of Orthopaedics at the University of Manchester and a Consultant Orthopaedic Surgery Consultant at Manchester University Hospitals NHS Foundation Trust. She is lead Clinician for Cartilage Repair and Regeneration, and has conducted research into the best techniques of clinical cartilage repair and the potential of the use of stem cells in articular cartilage repair.

Dr. Ross A. Dunne is a Consultant Later Life Psychiatrist at Greater Manchester Mental Health Foundation Trust and Clinical Director of the Greater Manchester Dementia Research Centre. He has been a Principal Investigator on over 25 commercial clinical trials of advanced therapeutics in dementia, is NIHR-CRN lead for Greater Manchester, and dementia theme lead for Health Innovation Manchester. He leads Brain Health Manchester, a multidisciplinary clinic focusing on primary and secondary prevention of cognitive decline, biomarker-based diagnosis, and individualised risk reduction.

Prof. Richard Body is Professor of Emergency Medicine at the University of Manchester, Honorary Consultant in Emergency Medicine and Group Director of Research & Innovation at Manchester University NHS Foundation Trust. He is also the lead for Business Engagement & Innovation for the School of Medical Science. Rick has a personal academic interest in analytical modelling, decision support, diagnostics, and the design and conduct of large observational cohort studies and late phase clinical trials.

1.3.3 Statistical advisers

[A.N. Statistician]

[A.N.O Statistician]

1.3.4 Clinical Trial Methodology

[CTU Team]

1.4 KEY WORDS: Insert relevant key words to describe the trial; no more than 6 phrases

Anakinra, delirium, fracture, neck of femur, hip, prevention

1.5 Trial Flowchart

1.6 BACKGROUND

Delirium

Delirium is a syndrome of disturbed alertness, orientation and arousal, complicated by neuropsychiatric abnormalities like paranoia and hallucinations. A single episode of delirium may permanently damage cognition(1) and increases the risk of dementia 3-fold over the following 3 years(2). Delirium is more common in older people and occurs in 20% of hospital inpatients and 40% of postoperative surgical patients, including those undergoing hip repair(3). Up to 90% of those who fracture their hip have underlying abnormalities in biomarkers for Alzheimer's disease (rising to 98% in those with known mild cognitive problems)(4).

Hip fracture

In the UK, 65,000 people fracture their hip every year(3). On average, 7% of these people will die within a month of their fracture. Postoperative delirium doubles the risk of death in the 12 months after fracture(5), especially if superimposed on pre-existing dementia(6). So, hip fracture is a major public health concern, both hastening dementia onset and causing premature death in those living with dementia. There is currently no treatment that prevents or shortens the duration of delirium, and no promising candidate. Delirium is often treated by addressing the underlying contributors (e.g. infection, pain, sedating medicines) and using sensitive nursing practice and clear communication. This can improve outcomes. However, after hip surgery, delirium impairs the early mobilisation and engagement with physiotherapy vital for good postoperative outcomes in dementia, like mobility and discharge to your own home.

Hip fracture types Fractures of the hip are divided into intra-capsular and extracapsular. The "capsule" refers to the fibrous tissue containing a rich blood supply to the head of the hip which envelops the hip joint (ball:*femoral head* and socket:*acetabulum*). Intra-capsular fractures have the potential to disrupt the blood flow to the femoral head and cause avascular necrosis, especially if they are *displaced*. This is one of the reasons replacement of the femoral head, and the acetabulum (its socket) is preferred in intracapsular fractures. Extracapsular fractures occur outside the capsule and are less likely to disrupt bloodflow, occuring as they do in very vascular "cancellous" bone. Thesee can be managed using a dynamic (or sliding) hip screw. Extracapsular fractres can also be subdivided into stable and unstable, depending on the radiographic appearance of the lesser trochanter fragment.

Four aspects of compliance with NICE recommendations have been combined into a single key performance indicator, KPI 3 (NHFD Report 2021):

1. Patients with a subtrochanteric femoral fracture should be managed with an intramedullary (IM) nail fixation.
2. Patients with A1 or A2 trochanteric fractures should receive fixation with an extramedullary fixation device, such as sliding hip screw (SHS) rather than with an IM nail.

3. Patients with a displaced intracapsular hip fracture should receive a cemented arthroplasty: either hemiarthroplasty or total hip arthroplasty (THA).
4. Cemented THA rather than hemiarthroplasty should be offered to patients with a displaced intracapsular hip fracture who normally walk independently out of doors with no more than the use of a stick, who are not cognitively impaired and are medically fit for anaesthesia and the procedure.

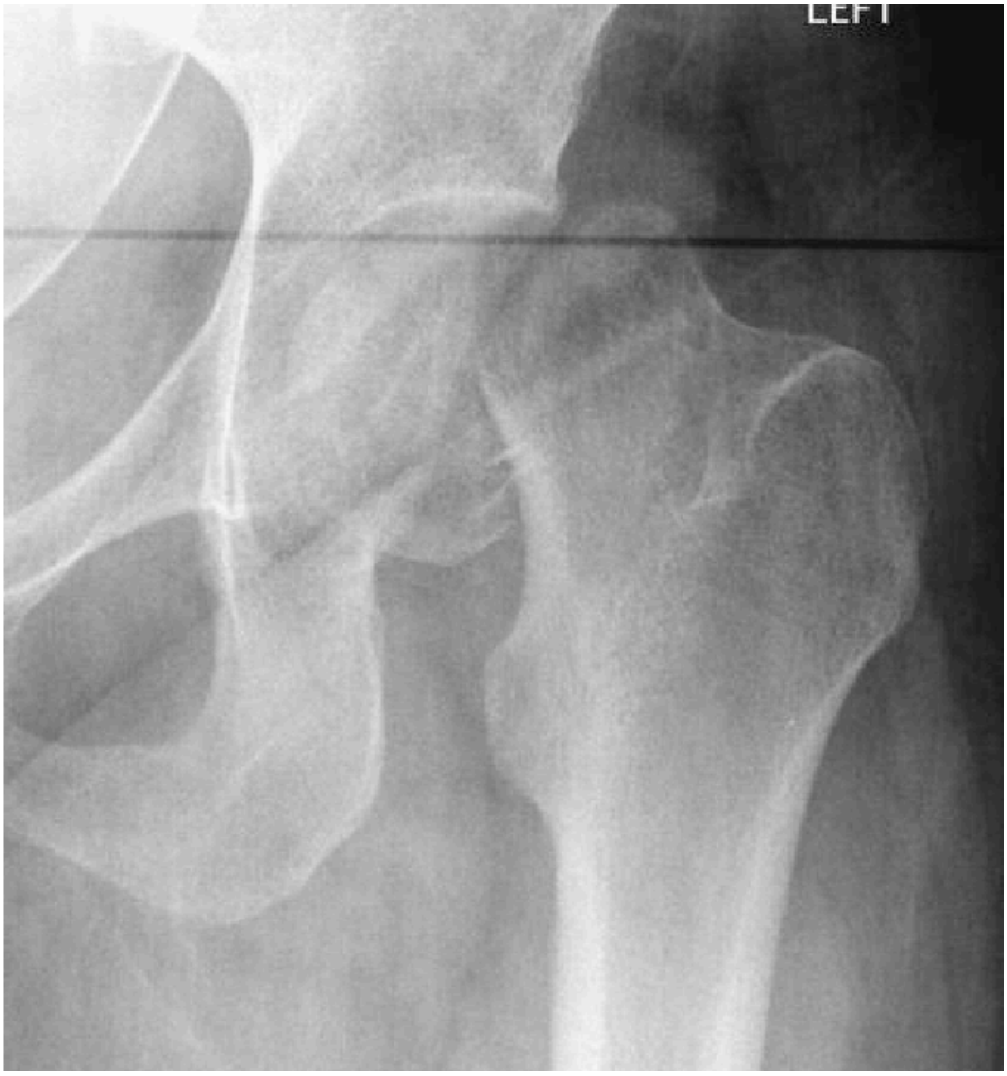

Figure 1: Displaced subcapital fracture

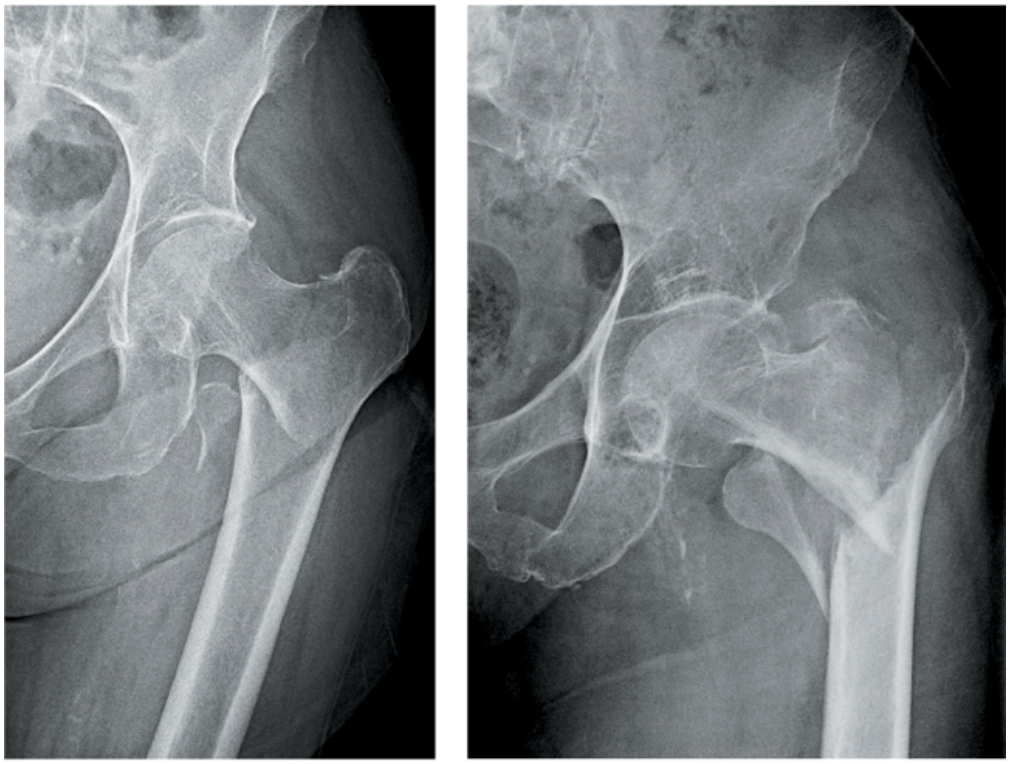

Figure 2: Stable (left) and unstable (right) extracapsular fracture

1.6.1 Review of existing evidence

Pre-clinical: IL-1 is a pro-inflammatory cytokine pivotal to the earliest stages of inflammatory response(7). It induces IL-6 and IL-8 gene expression and promotes lymphocyte differentiation and cellular immune response. The most prevalent preclinical model of delirium uses injection of bacterial lipopolysaccharide (LPS) to switch on the inflammatory cascade. IL-1 in isolation can mimic the cognitive effects of LPS in this model(8). Blockade of IL-1 action using recombinant receptor antagonists prevents the pro-inflammatory effects of LPS in these animal models of delirium(8). Thus, blockade of this early, amplifying step in the pro-inflammatory cytokine cascade may prevent cognitive deterioration.

Clinical: In humans, IL-1 is a key driver of neuroinflammation after hip fracture, with raised CSF and serum levels(9).

Anakinra is a specific IL-1 receptor antagonist (IL-1RA) already in use for patients with autoimmune disease including arthritis and those with critical lung disease due to COVID. It is an analogue of the naturally produced human IL1 receptor antagonist.

2 Choice of outcome measure

Table

2.0.1 Minimum clinically significant difference

The minmum clinically significant difference in any of the candidate delirium scales is not well established in the literature. It is clear that preventing cases of delirium will have significant positive economic outcomes for the NHS. Therefore, it would be possible to reason backwards from utilities to a minimum number of 'prevented' cases - delirium or "no delirium" as outcome measure. However, it is not clear that a reduction in the severity of delirium is associated with a shorter duration of delirium (intuitively appealing as that may be). It is also not clear that a reduction in the severity of delirium is associated with a shorter hospital stay per se, because no treatment has been found which effectively reduces severity. Therefore, we have chosen measures which seek to measure the primary outcome - delirium severity, and measure as secondary outcomes important clinical endpoints such as time-to-stand and time to medical fitness-for-discharge, because there are many confounding postoperative factors apart from delirium which might influence their outcome, significantly lowering the signal-noise ratio.

One advantage of the planned use of a Bayesian paradigm in the data analysis is that the research consumer (reader, reviewer, editor or future research groups) can establish from the multivariate posterior probability distribution the probability that Anakinra reduces delirium by a given number of points on th eoutcome scale, without this being pre-specified beforehand.

However, we have specified a minimum clinicalyl significant difference of 3 points for the purposes of randomisation weighting and allocation within the provisos of the Bayesian adaptive design.

Aim The aim of the research is to examine whether Anakinra can reduce the incidence of delirium post hip repair in older people. Anakinra is an interleukin-1 (IL-1) receptor antagonist licensed for the treatment of rheumatoid arthritis. It is given subcutaneously twice daily, ideal for inpatients with delirium who may not be able to take oral medications. We will conduct a double-blind randomised controlled trial of Anakinra in older people after hip fracture.

Objectives The objectives, in priority order, are to compare subcutaneous Anakinra to placebo given twice daily during the perioperative period in terms of: 1. (1°) Severity of delirium postoperatively as measured by the XXXXXXXX 2. (2°) Time to first weight bearing postoperatively 3. (3°) Time until medically fit for discharge postoperatively 4. (3°) Safety of Anakinra during the perioperative period and in wound healing 5. (3°) Tolerability of Anakinra versus placebo in terms of common side effects 6. (3°) Effect of Anakinra on 30-day mortality

Exclusion criteria: 1. Lack of a study partner or caregiver 2. Active infection 3. History of hypersensitivity to or unacceptable side effects of Anakinra 4. Current substance misuse 5. Active malignancy 6. Acute stroke or TIA 7. Currently participating in clinical trial of an investigational medicinal product (CTIMP) 8. Women of child-bearing potential 9. Neutropenia of any cause.

We plan to conduct this research in a sample of people presenting to the Emergency department at Wythenshawe hospital in South Manchester. Since 2017, Wythenshawe Hospital has been the regional orthopaedic trauma centre, and receives over 40 patients per month with hip fractures. The vast majority of these fractures occur in the over 65s, with a median age of 75. Higher energy injuries (for example, femoral fractures due to road traffic injuries in younger people) are usually triaged to the regional Major Trauma Centre at Manchester Royal Infirmary. Thus, the sample is pre-selected for older people with low-energy injuries, most often due to falls. Approximately 2/3 of hip fractures occur in women due to the increase in risk posed by postmenopausal osteopenia.

Anakinra

This is the first use of Anakinra or any IL1RA in the treatment or prevention fo delirium in humans. Only one study mentioning a posthoc analysis of the occurence of delirium or not in the treatment of COVID19 in the Intensive Care setting is available. This was a comparison to

2.1 RATIONALE

Our hypothesis is the reduction in CNS IL-1 levels caused by the administration of once daily Anakinra in the period before and after surgical repair of the fractured neck of femur will result in reduced severity of delirium in those with

2.2 Assessment and management of risk

This trial is categorised as: (delete as appropriate)

3 OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

3.1 Secondary objectives

3.2 Outcome measures/endpoints

3.3 Primary endpoint/outcome

3.4 Secondary endpoints/outcomes

3.5 Exploratory endpoints/outcomes

3.6 Table of endpoints/outcomes

Table 5: Trial outcomes

Objectives	Outcome measures	Timepoints
Primary Objective		

4 TRIAL DESIGN

5 TRIAL SETTING

6 PARTICIPANT ELIGIBILITY CRITERIA

Participation criteria have been chosen to be clear so that they can be applied consistently through the trial. Definitions for the timelines and flexibility of each eligibility criterion have been carefully considered to ensure that arbitrary or un-workable definitions have not been used.

6.1 Inclusion criteria

Participants capable of giving informed consent, or if appropriate, participants having an acceptable individual capable of giving consent on the participant's behalf. People of any gender are eligible People over 64 years of age at the date and time of presentation to the Emergency Department are eligible Radiologically confirmed femoral neck fracture as defined by the AO/OTA classification:

- A1: Simple pertrochanteric fracture
- A2: Multifragmentary pertrochanteric fracture/incompetence of the lateral wall
- A3: Intertrochanteric or reverse oblique fracture
- B1: Subcapital fracture
- B2: Transcervical fracture
- B3: Basicervical fracture
- C1: Split fracture
- C2: Depression fracture

6.2 Exclusion criteria

7 TRIAL PROCEDURES

7.1 Recruitment

7.1.1 Participant identification

7.1.2 Screening

7.1.3 Payment

7.2 Consent

7.3 The randomisation scheme (if randomised trial)

7.3.1 Method of implementing the randomisation/allocation sequence

7.4 Blinding

7.5 Emergency Unblinding

7.6 Baseline data

7.7 Trial assessments

7.7.1 Screening assessments

7.7.2 Baseline assessments

7.7.3 Assessment timepoints

7.7.4 Followup assessments

7.8 Long term follow-up assessments

7.9 Qualitative assessments

7.10 Withdrawal criteria

7.11 Storage and analysis of clinical samples (if details are provided in a laboratory/pathology manual there is no requirement to duplicate information in the protocol)

7.12 End of trial

8 TRIAL TREATMENTS

8.1 Name and description of investigational medicinal product(s)

8.2 Regulatory status of the drug

8.3 Product Characteristics

8.4 Drug storage and supply (if this included in a pharmacy manual then there is no requirement to duplicate information in the protocol)

8.5 Preparation and labelling of Investigational Medicinal Product

8.6 Dosage schedules

Anakinra is given twice daily subcutaneously. The maximum waiting time for surgical repair of fractured neck of femur is likely to be less than 48 hours, with 60$ of people having repair by the day following presentation to the Emergency Department. Therefore:

For those operated on the following day: {#tab-shortwait}

	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5
AM	Present	Rx 2	Rx 4	Rx 6	Rx 8	
		Repair (Short wait)	24h	48h	72h	
PM	Rx 1	Rx 3	Rx 5	Rx 7		

For those operated on within 48 hours: {#tab-longwait}

	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5
AM	Present	Rx 2	Rx 4	Rx 6	Rx 8	Rx 10
			Repair (Long wait)	24h	48h	72h
PM	Rx 1	Rx 3	Rx 5	Rx 7	Rx 9	

The number of doses of Anakinra given may differ between participants. 60% of participants are expected to have surgical repair within 24 hours (based on summary descriptive statistics from the National Hip Fracture Database). Therefore, we will continue to give doses of subcutaneous Anakinra twice daily for 72 hours after surgical repair.

8.7 Dosage modifications

Doses will be reduced if participants weigh under 50kg. For participants under 50kg a dose of Anakinra of 1.5mg/kg will be used. Protocol deviations due to missed doses will be treated as follows:

1. A.M. doses should be given at the usual time for A.M. medication for inpatients, usually between 8 and 9 a.m.
2. Doses given after 10 a.m. will be considered protocol deviations and recorded as such. The median time at A.M. and P.M. dosing will be recorded and reported in the trial report, as will the median duration between doses.
3. The A.M. Dose will be considered "missed" if it is not given by 12 noon that day. In these cases, this should be recorded as a protocol deviation and omitted. In these cases the participant will only receive the P.M. dose.

Intubation and I.V. sedation for any medical reason will render the measurement of delirium parameters impossible. Therefore, ICU admission, intubation or sedation with e.g. I.V Propofol will mean the participant receives no further doses of study medication or placebo, while the change in clinical status will be registered as a SUSAR.

Once a participant is withdrawn from the study, dosing with study medicine or placebo will not be reinitiated. As the treatment will only continue for the duration of the participant's hospitalisation, we expect there will be no reason for treatment breaks or drug-free holidays during the course of the study. There will be no cause for increasing doses after missed doses, nor will a dosing regime be extended because of a prolngewd stay in hospital.

The dose can not be modified due to participant or relative request. The dose can not be modified sue to clinician or professional request. **Local toxicity reactions with Anakinra are not common.**

Site reactions are common after prolonged dosing and usually result in inflammation, erythema and discoloration around injection sites. As trial participants will only be receiving 8 to 10 injections, and with the benefit of the rotation of sites, we do not anticipate site reactions which would result in either unblinding or discomfort for participants. If site reactions occur, they will be treated as per clinical guidance, by ensuring rotation of the injection site, providing pain relief and careful participant positioning. Site reactions will be reported as a Serious Adverse Event of Interest, but treatment may continue.

Anaphylactic reactions will be dealt with using the local anaphylaxis guidance for Manchester Foundation Trust, and referred for post-anaphylaxis care if possible at the Greater Manchester Rapid Access Anaphylaxis Clinic.

8.8 Known drug reactions and interaction with other therapies

8.8.1 Contra-indications (BNF)

Active infection; neutropenia (absolute neutrophil count less than 1.5 x 109/litre)—do not initiate; pre-existing malignancy

8.8.2 Cautions (BNF)

Elderly; history of asthma (increased risk of serious infection); history of recurrent infection; predisposition to infection

8.8.3 Interactions (BNF)

Abatacept: Anakinra is predicted to increase the risk of generalised infection (possibly life-threatening) when given with Abatacept. Manufacturer makes no recommendation. Severity:Severe; vidence:Theoretical

Bacillus Calmette-Guérin vaccine is predicted to increase the risk of generalised infection (possibly life-threatening) when given with Anakinra. UKHSA advises avoid (refer to Green Book). Severity:Severe; Evidence:Theoretical

Certolizumab pegol is predicted to increase the risk of generalised infection (possibly life-threatening) when given with Anakinra. Manufacturer advises avoid. Severity:Severe; Evidence:Theoretical

Etanercept: Anakinra is predicted to increase the risk of generalised infection (possibly life-threatening) when given with Etanercept. Manufacturer advises avoid. Severity:Severe; Evidence:Theoretical

Filgotinib: Filgotinib is predicted to increase the risk of immunosuppression when given with Anakinra. Manufacturer advises avoid. Severity:Severe; Evidence:Theoretical

Golimumab Anakinra is predicted to increase the risk of generalised infection (possibly life-threatening) when given with Golimumab. Manufacturer advises avoid. Severity:Severe; Evidence:Theoretical

Herpes-zoster live vaccine is predicted to increase the risk of generalised infection (possibly life-threatening) when given with Anakinra. UKHSA advises avoid (refer to Green Book). Severity:Severe; Evidence:Theoretical

Influenza vaccine (live) is predicted to increase the risk of generalised infection (possibly life-threatening) when given with Anakinra. UKHSA advises avoid (refer to Green Book). Severity:Severe; Evidence:Theoretical

Measles, mumps and rubella vaccine, live: is predicted to increase the risk of generalised infection (possibly life-threatening) when given with Anakinra. UKHSA advises avoid (refer to Green Book). Severity:Severe; Evidence:Theoretical

Rotavirus vaccine is predicted to increase the risk of generalised infection (possibly life-threatening) when given with Anakinra. UKHSA advises avoid (refer to Green Book). Severity:Severe; Evidence:Theoretical

Typhoid vaccine, oral is predicted to increase the risk of generalised infection (possibly life-threatening) when given with Anakinra. UKHSA advises avoid (refer to Green Book). Severity:SevereEvidence:Theoretical

Varicella-zoster vaccine is predicted to increase the risk of generalised infection (possibly life-threatening) when given with Anakinra. UKHSA advises avoid (refer to Green Book). Severity:Severe; Evidence:Theoretical

Yellow fever vaccine, live is predicted to increase the risk of generalised infection (possibly life-threatening) when given with Anakinra. UKHSA advises avoid (refer to Green Book). Severity:Severe; Evidence:Theoretical

8.8.4 Side-effects

Common or very common: Headache; infection; neutropenia; thrombocytopenia *further information*: Neutropenia reported commonly—discontinue if neutropenia develops.

Uncommon: Skin reactions

Frequency not known: Hepatitis

8.9 Concomitant medication

8.10 Trial restrictions

8.11 Assessment of compliance with treatment

8.12 Name and description of each Non-Investigational Medicinal Product (NIMP)

9 PHARMACOVIGILANCE

9.1 Definitions

9.2 Operational definitions for (S)AEs

9.3 Recording and reporting of SAEs, SARs AND SUSARs

9.4 Responsibilities

9.5 Notification of deaths

9.6 Pregnancy reporting

9.7 Overdose

9.8 Reporting urgent safety measures

9.9 The type and duration of the follow-up of participants after adverse reactions.

9.10 Development safety update reports

10 STATISTICS AND DATA ANALYSIS

10.1 Sample size calculation

10.2 Planned recruitment rate

10.3 Statistical analysis plan (summary)

Please see full Statistical Analysis Plan for reference

10.3.1 Summary of baseline data and flow of patients

10.3.2 Primary outcome analysis

10.3.3 Secondary outcome analysis

10.4 Subgroup analyses

10.5 Adjusted analysis

10.6 Interim analysis and criteria for the premature termination of the trial

10.7 Participant population

10.8 Procedure(s) to account for missing or spurious data

10.9 Other statistical considerations.

11 DATA MANAGEMENT

11.1 Data collection tools and source document identification

11.2 Data handling and record keeping (If this information is included in a data management plan then there is no requirement to duplicate this information in the protocol)

11.3 Access to Data

11.4 Archiving

12 MONITORING, AUDIT & INSPECTION

13 ETHICAL AND REGULATORY CONSIDERATIONS

13.1 Research Ethics Committee (REC) review& reports

13.2 Peer review

13.3 Public and Patient Involvement

13.3 Regulatory Compliance

13.4 Protocol compliance

13.5 Notification of Serious Breaches to GCP and/or the protocol

13.6 Data protection and patient confidentiality

13.7 Financial and other competing interests for the chief investigator, PIs at each site and committee members for the overall trial management

13.8 Indemnity

13.9 Amendments

13.10 Post trial care

13.11 Access to the final trial dataset

14 DISSEMINIATION POLICY

14.1 Dissemination policy

15 REFERENCES