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

Protocol version 0.01

Table of contents

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

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

IRAS
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: ……/……/…… Name (please print): Position:

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)	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	DMEC
	TSC

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	III
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

Trial Title	
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 twice 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

- 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.

- 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)

- 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

- Chief Investigator

The chief investigator will be the overall lead researcher for a research project. The hief 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.

1.2 Protocol contributors

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

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

1.4 Trial Flowchart

1.5 BACKGROUND

1.6 RATIONALE

1.7 Assessment and management of risk

This trial is categorised as: (delete as appropriate)

2 OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

2.1 Secondary objectives

2.2 Outcome measures/endpoints

2.3 Primary endpoint/outcome

2.4 Secondary endpoints/outcomes

2.5 Exploratory endpoints/outcomes

2.6 Table of endpoints/outcomes

Table 5: Trial outcomes

Objectives	Outcome measures	Timepoints
Primary Objective		

3 TRIAL DESIGN

4 TRIAL SETTING

5 PARTICIPANT ELIGIBILITY CRITERIA

5.1 Inclusion criteria

5.2 Exclusion criteria

6 TRIAL PROCEDURES

6.1 Recruitment

6.1.1 Participant identification

6.1.2 Screening

6.1.3 Payment

6.2 Consent

6.3 The randomisation scheme (if randomised trial)

6.3.1 Method of implementing the randomisation/allocation sequence

6.4 Blinding

6.5 Emergency Unblinding

6.6 Baseline data

6.7 Trial assessments

6.8 Long term follow-up assessments

6.9 Qualitative assessments

6.10 Withdrawal criteria

6.11 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 TRIAL TREATMENTS

7.1 Name and description of investigational medicinal product(s)

7.2 Regulatory status of the drug

7.3 Product Characteristics

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

7.5 Preparation and labelling of Investigational Medicinal Product

7.6 Dosage schedules

7.7 Dosage modifications

7.8 Known drug reactions and interaction with other therapies

7.9 Concomitant medication

7.10 Trial restrictions

7.11 Assessment of compliance with treatment

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

8 PHARMACOVIGILANCE

8.1 Definitions

8.2 Operational definitions for (S)AEs

8.3 Recording and reporting of SAEs, SARs AND SUSARs

8.4 Responsibilities

8.5 Notification of deaths

8.6 Pregnancy reporting

8.7 Overdose

8.8 Reporting urgent safety measures

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

8.10 Development safety update reports

9 STATISTICS AND DATA ANALYSIS

9.1 Sample size calculation

9.2 Planned recruitment rate

9.3 Statistical analysis plan

Aim: to fully describe the statistical analysis plan

9.3.1 Summary of baseline data and flow of patients

9.3.2 Primary outcome analysis

9.3.3 Secondary outcome analysis

9.4 Subgroup analyses

9.5 Adjusted analysis

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

9.7 Participant population

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

9.9 Other statistical considerations.

10 DATA MANAGEMENT

10.1 Data collection tools and source document identification

10.2 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)

10.3 Access to Data

10.4 Archiving

11 MONITORING, AUDIT & INSPECTION

12 ETHICAL AND REGULATORY CONSIDERATIONS

12.3 Regulatory Compliance

12.4 Protocol compliance

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

12.6 Data protection and patient confidentiality

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

12.8 Indemnity

12.9 Amendments

12.10 Post trial care

12.11 Access to the final trial dataset

13 DISSEMINIATION POLICY

13.1 Dissemination policy

14 REFERENCES