APPENDIX 13 to WHiTE Platform Master Protocol

World Hip Trauma Evaluation 13

Delirium and Cognitive Impairment (DeCI)

This appendix should be read with the accompanying WHiTE Platform Master Protocol. This appendix describes only the additional details relevant to the conduct of this particular randomised comparison within the context of the overarching master protocol. Based on Protocol Appendix Version 4.0, 24Mar2025.

For Master Platform please refer to

Costa, M et al. The World Hip Trauma Evaluation (WHiTE) platform trial: a framework for randomized comparisons of interventions for fragility hip fracture. Bone Jt. Open 2025 (Apr)2;6(4):383-390.

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PLAIN ENGLISH SUMMARY

This study has been designed following a James Lind Alliance Patient and Public Research Priority Setting Partnership, which identified the following question as a key research priority: "What are the best treatments to prevent and treat confusion and delirium after surgery in adults with a broken bone in the leg?" The study has been co-produced with the UK Musculoskeletal Trauma Patient and Public Involvement Group.

A broken hip (hip fracture) is a very serious injury that requires surgery to repair or replace the broken bone followed by a long period in hospital to recover. Around a quarter of patients with hip fracture die within a year and those that survive have a permanent loss of quality of life. Worldwide there are 1.3 million hip fractures each year, with more than 70,000 in the UK. Around a quarter of patients who have a hip fracture have an episode of 'delirium' around the time of their surgery. Delirium is a condition where the patient loses awareness of themselves and their environment, and has difficulty thinking clearly. For relatives and friends, as well as the patient, delirium is very disturbing. The symptoms of delirium are similar to those of patients with dementia but develop over a short period and tend to vary over time. In the short-term, delirium leads to longer stays in hospital and an increased risk of complications including death. In the longer-term, delirium is closely linked with an increased risk of developing dementia. Delirium is thought to be caused by inflammation in the brain. The inflammation is triggered by the injury and thought to get worse during surgery. This study will investigate a drug called infliximab which is given during surgery. Infliximab is a powerful anti-inflammatory drug. The aim of this study is to decide if patients who have operations on broken hips are less likely to have delirium, if we treat them with infliximab during the operation.

This study is open to all patients aged over 60 years with a hip fracture, apart from the very small number of patients who do not have an operation on their hip. Eligible patients will be approached for recruitment before their treatment where possible. Patients who are unable to consent for themselves may take part in the trial with the agreement of their relatives or an independent doctor. Patients at approximately 8 hospitals in the UK will be approached to take part in the study. 564 participants will take part, with half being allocated by chance to receiving infliximab, and half to receiving a placebo containing no infliximab. Neither the patients nor their doctors will know which treatment they had to make the study fair. All other elements of the patients' treatment will follow the normal care pathway for all hip fracture patients at the hospital.

We will use a simple questionnaire to measure symptoms of delirium in the first five days after surgery. We will also assess the patients' mobility, quality of life and complications, including the risk of infection and of developing dementia in the 12 months after surgery. Some participants may also consent to have their brain waves monitored during surgery and to have small blood samples taken before and in the days after surgery to measure the level of inflammation in the blood.

The results will be presented at scientific meetings and published internationally. Patient representatives will produce a lay summary and take the results to patient advocacy groups and spread the information through social media.

1 BACKGROUND AND RATIONALE

1.1 What is the clinical problem being addressed?

Delirium is a common neuropsychiatric syndrome defined as disturbance of attention, awareness and cognition which develops over a short period of time, represents a change from baseline and tends to fluctuate during the course of the day.[1] Older patients with hip fracture are at particularly high risk of developing post-operative delirium due to the physiological stress and inflammation from the injury, pain and associated analgesia, and the surgery required to treat the broken bone. UK national audit data for 2018 showed that 25% of all patients with hip fracture suffered with post-operative delirium.[2] As well as being distressing for patients and their families, post-operative delirium is associated with poor functional outcomes, reduced quality of life, longer hospital stays and increased mortality.[3,4] People with hip fracture admitted from their own home who develop delirium are twice as likely to die while in hospital, and nearly four times more likely to need placement in a nursing home, compared to those who do not develop delirium in the post-operative period. Furthermore, post-operative delirium is also closely associated with long-term cognitive impairment.[5,6]

In this trial we will investigate if an infusion of the anti-TNF agent infliximab during surgery, has an effect on delirium symptoms in the immediate post-operative period and on the development of cognitive impairment, quality of life and mortality in the following year.

1.2 How does the existing literature support this proposal?

The inflammatory response following surgery is associated with the development of delirium and long-term cognitive impairment. The cytokines released in the periphery as a result of the surgical trauma lead to increased permeability of the blood brain barrier,[7] ingress of activated monocytes and activation of the microglia, which lead to neuronal injury and delirium.[3] Although a wide variety of inflammatory mediators have been implicated in the development of delirium, there is compelling evidence that many of the effects are mediated by TNF.[8] In patients undergoing coronary artery bypass grafting, post-operative TNF levels were found to be raised in the group who developed delirium,[9] and in a series of 148 patients, including 75 cases with fractures, surgery was associated with increased levels of circulating TNF, with a positive correlation of TNF and IL-6 levels and the development of delirium.[10] A study of cytokines in the systemic circulation and the CSF in patients aged ≥55yr undergoing knee surgery found no change in TNF levels at 3 hours and beyond post-surgery, although IL-6 was increased in both blood and CSF.[11] However, TNF is released within a few minutes of commencement of surgery and has a relatively short half-life of approximately 30 min in the circulation. Therefore, timing of blood sampling is crucial. In a group of 124 patients aged ≥70years undergoing hip arthroplasty under epidural anaesthesia, there was an increase in plasma TNF levels 30 min after anaesthesia.[12]

Raised levels of TNF are also associated with impaired cognitive function in non-surgical patients. In a series of 300 patients with mild to severe Alzheimer's disease, raised serum TNF levels were associated with increased neuropsychiatric symptoms characteristic of sickness behaviour, independent of delirium.[13] Furthermore, acute systemic inflammatory events in patients with Alzheimer's disease were associated with higher circulating TNF levels and increase in cognitive decline.[14] Higher levels of TNF and IL-6 were associated with smaller hippocampal volume on magnetic resonance imaging scan in 28 older adults. [15]

Various strategies have been used in an attempt to reduce post-operative cognitive dysfunction[16] and act, at least in part, by reducing TNF levels. They include modification of anaesthetic agents[17] as well as ancillary treatments that also have been shown to result in diminished pro-inflammatory cytokine levels, including

TNF. Whilst the use of regional anaesthesia is not associated with lower levels of circulating proinflammatory cytokines compared to general anaesthesia,[18] volatile anaesthetic agents such as sevoflurane have been associated with elevated serum TNF and IL-6 and a higher incidence of delirium in elderly patients undergoing surgery.[19] In a cohort of older patients undergoing laparoscopic cholecystectomy, use of isoflurane or sevoflurane resulted in higher levels of circulating TNF, IL-1β and IL6, and an increased incidence of delirium.[20] Low dose dexmedetomidine, which is licensed for use as a sedative, resulted in reduced incidence of delirium and lower circulating TNF levels in older patients undergoing hip arthroplasty,[21] and a meta-analysis of 15 randomised control trials confirmed that administration of dexmedetomidine resulted in reduction of circulating TNF, IL-1β and IL-6.[22] A recent review highlighted the evidence for dexmedetomidine reducing levels of TNF in patients with delirium.[8] Administration of hypertonic saline resulted in a reduction in the risk of development of post-operative delirium and was associated with a significant reduction in circulating TNF levels in patients undergoing surgery for fractured neck of femur.[23] A trial comparing parecoxib, a selective COX-2 inhibitor, with placebo found reduced incidence of delirium in elderly patients undergoing knee arthroplasty and was associated with reduced levels of TNF, IL-6 and IL-β in the circulation.[24] Similar results were reported in a trial of celecoxib.[25]

Whilst there have been no trials to assess the efficacy of anti-TNF in reducing delirium and cognitive impairment in patients undergoing surgery, there are data showing improvement in cognitive function, mood, pain and sleep in patients with systemic inflammatory disorders receiving anti-TNF. Patients with rheumatoid arthritis treated with adalimumab showed improvement in cognitive function[26] and infliximab treatment in patients with rheumatoid arthritis resulted in improvement in sleep and alertness disturbance, which were unrelated to amelioration of joint tenderness, swelling and morning stiffness.[27] A study of patients with sarcoidosis found cognitive impairment in 35% of patients compared to 14% of controls, and treatment with infliximab or adalimumab resulted in significant improvement in cognitive function compared to those treated with steroid with or without methotrexate.[28] A phase 3 trial of 618 patients with mild to moderate psoriasis found significant improvement in depression in the group treated with etanercept.[29] Importantly, this was unrelated to indices of disease activity, including clearance of skin lesions or joint pain. A nested case-controlled study of 8.5 million insured adults in the USA found that there was an increased risk of development of Alzheimer's disease in patients with rheumatoid arthritis that was significantly reduced in patients treated with etanercept. A trial of infliximab found improvement in depression in patients with high baseline levels of inflammatory cytokines, including circulating TNF.[30] A trial of adalimumab showed improvement in pain and depression in patients with moderate to severe hidradenitis suppuritiva.[31] Sleep disturbances have also been shown to improve following anti-TNF. A randomised trial of etanercept showed improvement in sleep pattern in patients with alcohol dependence.[32] Similarly, in patients with high baseline inflammation and treatment resistant depression, infliximab led to improved sleep continuity.[33]

Based on the above evidence, our hypothesis is that TNF released by immune cells recruited to the site of surgery crosses the blood-brain barrier to activate resident microglia. It also increases permeability of the blood-brain barrier to allow ingress of circulating activated monocytes. This leads to neuronal damage, which is manifest as delirium.

1.3 Need for this comparison

Avoiding post-operative delirium is a priority for the NHS; reducing delirium is a 'Key Performance Indicator' for the UK NHFD and is linked to Best Practice Tariff payments in England. Delirium is a

devastating acute neuropsychiatric syndrome, common in people with hip fracture, and associated with adverse outcomes. Despite this, there are no treatments to prevent or ameliorate delirium, in part due to our poor understanding of the underlying biology.

A recent NIHR James Lind Alliance Research Priority Setting Partnership, identified: "*What are the best treatments to prevent and treat confusion and delirium after surgery in adults with a fragility fracture of the lower limb?"* as a key research priority. It also addresses a key research question in the forthcoming Association of Anaesthetists' guidance on perioperative management of hip fracture: "*What are the best anaesthetic interventions to prevent and treat confusion and delirium after surgery for hip fracture?"* This proposal falls within the remit of the current NIHR *injuries, accidents and urgent and emergency care* themed call, in particular the management and treatment of the commonest major injury in older people.

The overarching aim of the WHiTE Platform Study is to improve the care of patients with a fracture of their hip. Delirium delays patients' recovery and puts them at greater risk of complications so reducing the severity of delirium is an important component of the platform.

2 OBJECTIVES AND OUTCOME MEASURES

2.1 Primary objective

To compare peak delirium in the 5 days following hip fracture surgery between the treatment groups.

2.2 Secondary objectives

1. To compare cognitive impairment scores at 4 and 12 months post-diagnosis of a hip fracture between the treatment groups.
2. To compare health-related quality of life at 4* and 12 months post-diagnosis of a hip fracture between the treatment groups.
3. To compare mortality risk within the first 12 months post-diagnosis of a hip fracture between the treatment groups.
4. To compare mobility at 4* and 12 months post-diagnosis between the treatment groups.
5. To compare residential status at 4* and 12 months post-diagnosis of a hip fracture between the treatment groups.
6. To compare the risk and pattern of complications at any point within the first 12 months post-diagnosis of a hip fracture between the treatment groups.
7. To compare the healthcare and broader resource implications between the treatment groups.

* Objectives at these timepoints are collected as part of the overarching Platform.

2.3 Exploratory mechanistic objectives

The following objectives will be investigated through analysis of blood samples and analysis of EEG recordings.

i) To investigate the role of TNF in the development of delirium and explore the effect of treatment with anti-TNF through blood sample analysis.

ii) Explore which EEG patterns are associated with neuronal inflammation as measured on blood biomarkers, and whether this association with neuronal inflammation is attenuated by the administration of anti-TNF during surgery.

iii) Explore whether EEG patterns that correlate with inflammation are predictive of the development and severity of delirium.

Blood sample collection and the collection of EEG recordings will only be conducted in a subset of recruitment centres based on research team capacity and availability of relevant equipment. The collection of data for the exploratory objectives will take part during the internal pilot phase (defined as the recruitment of the first 120 patients, see section 8.1). Consent to provide blood samples and/or EEG recordings for the exploratory mechanistic objectives will be optional for participants.

2.4 Outcome measures

The common outcome data described in the Platform Master Protocol will be collected and augmented with additional data collection during the first five days during and after hip fracture surgery and at 4- and 12-months post-diagnosis of a hip fracture. Additional outcomes specific for this randomised comparison are:

7.4.1 Post-operative delirium

Peak post-operative delirium will be measured by the ***MDAS.*** Participants will be assessed once daily after the surgical repair of the hip fracture using the MDAS[34] from day 1 to day 5. The MDAS is a validated scale which quantifies the severity of delirium based on 10 features which integrates behavioural observations with objective cognitive testing. MDAS generates a scale from 0 to 30 (30 is most severe) and can be completed by trained research staff in 5 minutes or less[4]. The peak MDAS score will be the maximum recorded score reflecting the worst and most delirious state of the participants in the first five days after surgery.

In addition to the expertise and experience within the research team, we sought advice from several external sources with regard to the choice of primary outcome measure in this trial. While several other assessment tools were considered, MDAS has been used widely in previous trials, including large trials in the hip fracture population. The peak MDAS recorded in the 5 days following surgery provides a comprehensive assessment of the severity of delirium, integrating behavioural observations with objective cognitive testing.[35] Furthermore, MDAS is based upon the diagnostic criteria for delirium in the Diagnostic and Statistical Manual of Mental Disorders; the 10 MDAS features being: reduced level of consciousness/awareness, disorientation, short-term memory impairment, impaired digit span, reduced ability to maintain and shift attention, disorganised thinking, perceptual disturbance, delusions, decreased or increased psychomotor activity, and sleep-wake cycle disturbance. Another key consideration was the feasibility of training staff to use the delirium assessment tool in the context of a large-scale trial. We believe that the peak MDAS in the first five days following surgery will provide a comprehensive assessment of delirium, without requiring extensive training and/or specialist staff to administer it.

The minimum clinically important difference of 2.5 on the 30-point scale, and the Standard Deviation for the peak MDAS in the post-operative period of 7.0, was established specifically in patients with hip fracture.[4] The decision to adopt a Minimal Clinically Important Difference (MCID) of 2.5 using the full scale of the MDAS tool (c.f. a cut-off score) was made based upon a review of the literature and direct discussions and the recommendation of Ed Marcantonio, Professor of Medicine at Harvard, who has investigated this area extensively.

7.4.2 Cognitive impairment

Patients will complete the TICS UK English 2014 questionnaire to assess Cognitive Impairment at 4 and 12 months post-diagnosis of a hip fracture. Since most people treated for a hip fracture in the UK are not followed-up in person after being discharged from hospital, TICS questionnaire is the best tool in this setting. A 3-point difference in TICS score (score=0-41, with lower scores indicating cognitive impairment) is considered clinically significant.

7.4.3. Complications

The expected complications for the comparison are detailed in section 11.1 of this protocol appendix. To facilitate collection of complications as per the Platform Master Protocol, medical records for all participants will be reviewed by appropriately trained staff for indicators of wound infection at discharge. In addition to the Platform follow-up time points, at 12 months post-diagnosis of a hip fracture, the participants will self-report (via telephone interview, electronic media or postal questionnaire) on signs of infections. For those participants lacking capacity, an appropriate proxy will be asked to provide this information. In rare cases, where participants or carers cannot be contacted, information with regards symptoms/treatment for infection will be obtained from the participant's GP and/or recruitment centre.

Upon indication of potential signs of infection in the participant report at 4 months, the recruitment centre/GP will be contacted and asked to review the participant's medical records to provide additional information. Due to its severity, diagnosis of a 'deep infection' will always be documented in the participant's medical records.

The following outcome measures will only be collected in a subset of recruitment centres and where patients have consented to their collection:

7.4.4 Blood samples

10ml blood samples will be collected at baseline, 30 minutes following the start of surgery, 24, 48 hours and 5 days post-surgery in red BD™ vacutainers. The blood will be centrifuged and serum aliquots stored locally at recruitment centres until shipment to the University of Oxford for analysis.

7.4.5 EEG recordings

The non-invasive electrodes will be applied to the participant's head before the start of surgery and intraoperative EEG recordings will be taken. EEG data will be collected as raw data. The EEG recordings will be transferred to the University of Oxford via secure file transfer for analysis.

3 DESIGN

3.1 Concept

This is a multi-centre, two-arm placebo-controlled randomised comparison embedded within the overarching WHiTE Platform testing clinical superiority between the treatment groups with embedded exploratory mechanistic outcomes.

This will be a two-phased comparison. Phase 1 (internal pilot) will confirm the expected rate of recruitment and acceptability of procedures in 4 UK hospitals. Phase 2 (main phase) will extend the randomised comparison for a total of approximately 8 hospitals.

Internal Pilot

The internal pilot phase is defined as the period during which the first 120 consecutive participants are consented into the study. It is anticipated that the internal pilot will take place over a period of 6 months. Screening logs will be kept at each recruitment centre to determine the number of patients assessed for eligibility and reasons for any exclusion. The number of eligible and recruited patients, and the number of patients who decline consent or withdraw will be recorded. The Data Safety Monitoring Committee (DSMC) and Platform Oversight Committee (POC) will closely monitor recruitment in order to make a recommendation regarding continued progress of the comparison against the specified stop/go criteria. If the comparison is stopped due to feasibility not being shown, then all participants will be followed up per protocol. If the comparison continues into the main phase, participants from the internal pilot will be included in the final analysis.

Data collection for the exploratory mechanistic outcomes will be conducted during the internal pilot phase only.

Main phase

During the main comparison phase, the remainder of the target 564 participants will be recruited. Participants will be allocated on a 1:1 basis to either placebo or infliximab infusion treatments.

Assessments will include all those described in the Platform Master Protocol, augmented with additional data relevant to this specific randomised comparison. In summary:

Routine pre-operative cognitive assessment will be made using the delirium screening tool 4AT; these scores are used throughout the UK as part of routine admission clinical practice. Similarly, as part of routine care, full blood counts are taken pre-operatively; we will record the haemoglobin concentration taken on admission from electronic records. Further baseline demographic data including pre-injury mobility and residential status will be collected.

Participants or their proxies will also be asked to complete the EQ-5D-5L to indicate their typical pre-injury quality of life status.

The primary outcome is post-operative delirium recorded using the peak MDAS which will be recorded each day during the first five days after surgery.

At 4- and 12-months post-diagnosis of a hip fracture, cognitive impairment using TICS, EQ-5D-5L, residential and mobility status, complications and participant-completed resource use questionnaires will be collected by the central research team at the University of Oxford. We will adopt the techniques used in the previously conducted WHiTE Cohort study to collect self-reported or proxy-reported information.

4 STUDY PROCEDURES

A study flow chart is provided in Annex A.

4.1 PARTICIPANT IDENTIFICATION

9.1.1 Comparison participants

A subset of participants in the overarching WHiTE platform will be eligible for this randomised comparison.

9.1.2 Inclusion criteria

As per the overarching Platform Master Protocol; all adults aged 60 years or over diagnosed with a hip fracture that in the opinion of the treating surgeon may benefit from surgical treatment.

9.1.3 Exclusion criteria

In addition to the exclusion criteria stated in the overarching platform protocol, a patient is not eligible if ANY of the following apply:

1. The patient has severely impaired renal function eGFR <30 ml.min-1
2. The patient has severely impaired hepatic function
3. The patient is currently taking any anti-TNF drug
4. The patient has a contra-indication to anti-TNF injection
5. The patient has a known hypersensitivity to any anti-TNF agent or any of the excipients

6. The patient has known active tuberculosis (TB) or history of TB or at risk of developing TB e.g. through the use of immunosuppressants
7. The patient has another known active infection (chronic or localised) or known history of recurring infections or condition which may predispose patients to infection, including the use of concomitant immunosuppressive medications
8. The patient has known lung fibrosis
9. The patient had systemic inflammatory disorder such as rheumatoid arthritis or inflammatory bowel disease
10. The patient has known moderate to severe heart failure (NYHA class III/IV)
11. The patient has HIV, Hepatitis B or C (based on medical history)
12. The patient is at risk of Hepatitis B or HIV infections, including intravenous drug use
13. The patient has been diagnosed with Multiple Sclerosis (MS) or other central or peripheral nervous system demyelinating disorders
14. History of malignancy within five years prior to screening or any evidence of persistent malignancy, except basal cell or squamous cell carcinomas of the skin, or cervical carcinoma in situ which has been treated or excised in a curative procedure.
15. The patient has had a live vaccination 4 weeks prior to study entry or will require one within 12 weeks after the study intervention
16. The patient takes biologics including anakinra or abatacept or DMARDS
17. The patient is or has been a participant in a clinical trial of a medicinal product in the last 12 weeks

Pre-operative radiographs of the chest are routine in this patient group. Participants with a history of TB or signs of TB on the chest radiograph will be excluded from enrolment in the study. This is in line with UK guidelines that a chest radiograph is used for screening patients who are to be commenced on regular anti-TNF therapy.[36]

Eligibility for entry into the comparison will be confirmed by a medically qualified person.

4.2 Consent

Patients will be presumed to have capacity unless established otherwise and the default will be to seek prospective individual consent from every patient. Where patients do not have capacity, those procedures laid down in the Platform Master Protocol will apply.

Where participants are recruited in a recruitment centre that is taking part in the collection of the exploratory mechanistic outcomes, they will be provided with the option to consent to having their EEG recordings and blood samples being collected.

For participants who do not have capacity at the time of consent, the Legal Representative will be given the option to consent for the EEG recordings and blood sample collection. Should the participant regain full capacity during the first 5 days post-surgery, they will be provided with information about the collection of blood samples. Written consent for this optional part of the protocol will then be sought from the participant. A copy of the consent form will be stored in the participant's medical notes. If the participant does not wish for any further blood samples to be collected, a note will be made in the participants' medical record and study record that no further samples will be collected.

With regard to these provisions, the randomised comparison described in this appendix **is** a CTIMP.

4.3 Randomisation

Randomisation will be as per Platform Master Protocol. Randomisation will be on a 1:1 basis to infliximab or placebo, stratified by recruitment centre and the presence/absence of cognitive impairment at presentation. The allocation sequence will be generated by the trial statistician using variable block sizes and stored securely in a web-based encrypted system provided by OCTRU. Full details will be stored in a separate randomisation and blinding plan stored in the confidential statistics section of the trial master file.

Randomisation will be performed as close to the time of induction of anaesthesia as possible to avoid the risk of postponement of surgery or moving to a different theatre list.

4.4 Blinding and code-breaking

This is a double-blinded comparison, whereby the participant and the local research team members involved in the delirium assessment and data collection process will be blinded to the allocated treatment. An appropriately qualified anaesthetist will prepare the comparison medications following randomisation.

Unless specifically requested, participants in this comparison will not be informed which of the two treatments they have received. No formal assessment of the success or otherwise of the blinding will be made. Participants who request information with regards the treatment they received, will be informed at the end of the follow-up period or at the point of withdrawal from this randomised comparison.

A 24 hour emergency unblinding function will be available via the secure online randomisation system to reveal which treatment a participant has been allocated to, should this be required. However, the emergency scenario will always be managed using the applicable local and national policy and guidelines, which will not require staff to carry out unblinding first.

Unblinded information will be provided if one or more of the following criteria is satisfied:

1. Emergency circumstances
2. Other reason (non-emergency)

No CI's approval is required if the reason for unblinding is 1 above. If the reason for unblinding is 2, CI's approval will be required first.

As all emergency cases would not require immediate unblinding, no out of hours contact is appointed.

The members of the central trial team who are authorised to unblind participants will be listed in a Trial Specific Instructions Unblinding Annexe document. Request for unblinding from the research teams or PI will be forwarded to an authorised member of the central trial team. If the person requiring the unblinding is not the PI then that health care professional will notify the Investigating team that an unblinding is required for a trial participant and an assessment to unblind should be made in consultation with the clinical and research teams. The authorised members of the team will follow the randomisation system user guide for unblinding as detailed in relevant OCTRU SOP.

On receipt of the treatment allocation details the PI or treating health care professional will continue to deal with the participant's medical emergency as appropriate. The PI will document the breaking of the code and the reasons for doing so in the investigator site file and medical notes. It will also be documented at the end of the comparison in any final comparison report and/or statistical report. The unblinded

information and any related correspondence will be stored in a password protected subfolder in the eTMF in the patient's subfolder accessible only to authorised member of the central trial team.

The CI will notify the Sponsor in writing as soon as possible following the code break detailing the necessity of the code break. The CI will also notify the relevant authorities. The written information will be disseminated to the DSMC for review in accordance with the DSMC Charter.

4.5 Assessments

9.5.1 Schedule of assessments

The overall schedule of assessments, including the common outcome set and the additional outcomes measured for this comparison, and methods for data collection are described in the table below:

Time Point	Data	Source	Setting
Pre-surgery*	i) 4AT ii) pre-operative haemoglobin levels iii) 10 ml pre-surgery blood sample**	Participant (blood sample: participant only)	Acute inpatient - face to face;
Baseline^	i) Demographics ii) Relevant medical history iii) Injury details Pre-injury (retrospective): iv) HR-QoL v) Residential status vi) mNMS vii) Resource use viii) Opioid use	Participant or proxy & medical record	Acute inpatient - face to face; medical record review
Surgery**	i) Intra-operative analgesia ii) 10 ml blood sample within 30 minutes of start of surgery iii) Intra-operative EEG recordings	Anaesthetic chart Participant	Medical record review Acute inpatient
Days 1-5 post-surgery*	i) MDAS ii) Opioid analgesia use iii) 10 ml blood sample at 24 and 48 hours and day 5 post-surgery **	Participant Medical records	Acute inpatient - face to face; Medical record review
Up to point of discharge	i) Early complications	Medical records	Medical record review
4 months post-diagnosis of a hip fracture	i) HR-QoL ii) TICS* iii) Complications iv) Residential status v) mNMS vi) Resource use	Participant or proxy & medical record if indicated	Telephone, online or postal

12 months post-diagnosis of a hip fracture *	i) HR-QoL ii) TICS iii) Complications iv) Residential status v) mNMS vi) Resource use	Participant or proxy	Telephone, online or postal

Table 1: Assessment schedule, instruments and means of collection.

*Key: ^Baseline information will be collected before surgery where possible, otherwise it will be collected as soon as possible after. *Indicates measurement timepoint or data collected is in addition to the Platform Common Dataset specified in the Platform Master Protocol **indicates samples to be collected only by those centres participating in the mechanistic outcomes on participants where consent for this optional data collection has been obtained. Greyed out sections indicate data collected as part of the overarching Platform*

9.5.2 Visits and Contacts

Contact 1: Pre-operatively, 4AT will be collected on the hospital ward to determine baseline cognitive function and the presence or absence of delirium. Pre-operative haemoglobin levels will be recorded from medical records as a potential biomarker for prediction of delirium for the mechanistic outcomes.
A 10 ml blood sample will also be collected from consented participants in those centres participating in the exploratory mechanistic part of the protocol as reported in section 9.2.

Contact 2: Baseline data collection as per Platform Master Protocol.

Contact 3: During surgery: EEG recordings will be taken throughout surgery from consented participants in those centres participating in the exploratory mechanistic part of the protocol. For patients whose EEG recording will be recorded, a list of the anaesthetic drugs received intraoperatively will also be collected. A 10 ml blood sample will be collected from consented participants in those centres participating in the exploratory mechanistic part of the protocol at 30 mins after start of surgery.

Contacts 4-8: Days 1-5 after the day of surgery, delirium assessments will be made on the hospital ward by trained staff using the MDAS. Opioid use will also be collected. Ten ml blood samples will be collected from consented participants in those centres participating in the exploratory mechanistic part of the protocol at 24 and 48 hours and on day 5 post-surgery.

Contact 9: Follow-up at 4 months post-diagnosis of a hip fracture as per Platform Master Protocol with the addition of TICS.

Contact 10: Follow-up at 12 months post-diagnosis of a hip fracture, will be completed directly with the participant or a proxy either via telephone interviews by a member of the central research team, or through electronic means (electronic questionnaire/survey) depending on choice expressed by the participant or proxy at the time of consent.

4.6 Mechanistic Outcomes Analysis

9.6.1 Blood samples

The main objective of the mechanistic work will be to investigate the mechanisms leading to the development of delirium, specifically the levels of proinflammatory cytokines released by the innate immune cells, the chemokines which recruit these cells to the site of surgery and the efficacy of infliximab in blocking these pathways. Markers of monocyte/macrophage activation, blood-brain barrier

permeability and the degree of neuronal damage will be measured, as well as the effect of infliximab on all these processes.

Only a select number of recruitment centres will take part in the mechanistic data collection. Blood samples for the analyses will be collected and serum aliquots stored by the centres at 5 timepoints during the first 5 days of surgery:

- Pre-surgery
- At 30 minutes following start of surgery (+/- 15 minute window)
- 24 hours post-surgery (+/- 12 hour window)
- 48 hours post-surgery (+/- 12 hour window)
- Day 5 post-surgery (+/- 36 hour window)

The hypothesis is that circulating TNF released by inflammatory cells, including neutrophils and pro-inflammatory macrophages, recruited to the site of surgical 'injury', increases the permeability of the blood brain and promotes the ingress into the brain of activated monocytes and activation of resident microglia. This in turn leads to neuronal damage,[37,38] post-operative delirium and cognitive impairment. It will be tested whether this pathway can inhibited by perioperative administration of infliximab, which binds and inactivates the TNF. TNF is released immediately on commencement of surgery and has a short half-life of 30 min in the circulation, being detectable only within 1 hour of the surgery but not at 3 hours or later. Therefore, the infusion of infliximab in the anaesthetic room will commence before surgery and will continue for the total duration of the surgery. The duration of the surgery is on average 1 hour, and very rarely more than two. Infliximab has a half-life of 8 days. Therefore, the proposed dosage regimen will permit full target engagement.

The following analysis/assessments are planned on all available samples:

1. Measurement of serum markers of activation of the TNF system [soluble TNF Receptor1 (sTNFR1), soluble TNF Receptor2 (sTNFR2)] and proinflammatory cytokines downstream of TNF [interleukin-6 (IL-6), interleukin-1β (IL-1β)].

2. Quantifying serum levels of the chemoattractant molecules interleukin-8 (IL-8 or CXCL8) and monocyte chemoattractant protein-1 (MCP-1 or CCL2) that maintain the immune response.

3. Determining serum markers of monocyte/macrophage activation (sCD14, sCD163) and indices of overall inflammatory status [interleukin-10 (IL-10), C-Reactive Protein (CRP)].

4. Determining indices of blood-brain barrier integrity by measuring serum levels of E-selectin, angiopoietin 2, syndecan-1 and the ratio NSE: S100 calcium binding protein β (S100β).

5. Assessing neuronal damage by measuring levels of S100β released by damaged astroglial cells, NSE released by neurones and neurofilament light chain (NFL) released by injured axons and correlate these with the MDAS.

9.6.2 Blood Sample handling for comparison purposes

At each sample collection time-point, 10ml of blood will be drawn into a vacutainer and subsequently centrifuged. The serum will be divided into aliquots and frozen immediately at ≤-20^{o} C at the recruitment centre. Once the storage box is filled to capacity these will be couriered to Kennedy Institute at the University of Oxford along with the sample tracking form. Details of the assays, documentation and sample

analysis will be provided in the relevant laboratory SOP. For the purposes of analysis to determine the mechanistic outcomes, the samples will be analysed within the duration of the ethical approval for this comparison.

Samples will be pseudo-anonymised using a coded label containing a constant reference ID, a partial randomisation number, and reference numbers to the timepoints and aliquots collected.

9.6.2.1 Blood Sample handling for long-term storage

Participants for whom samples will be collected, will be asked to provide (or a legal representative) informed consent approving long-term storage, and future use of tissue and blood. As new mechanisms of action, safety and efficacy may evolve during or following the comparison, which are unknown at present.

Any remaining biospecimens from participants who have not consented to long-term storage will be destroyed at the end of the comparison as per Kennedy Institute at the University of Oxford SOPs.

Biospecimens, for which consent to long-term storage has been provided, will be anonymised and stored for a maximum of 15 years from the end of comparison at the Kennedy Institute at the University of Oxford, along with a blank copy of the comparison consent form and a letter from the Chief Investigator affirming that consent had been obtained appropriately using the form provided for these purposes. Any remaining biospecimens will be destroyed at the end of the long-term storage period.

9.6.3 EEG recordings

The first aim of this mechanistic work would be to quantify the occurrence of EEG patterns of cerebral vulnerability which correlate with the severity of postoperative delirium. The second aim will be to correlate the EEG patterns with measurement of neuroinflammation using blood biomarkers in the early postoperative period. By establishing the link between markers of neuronal inflammation and the pattern of the brains electrical activity at the time of surgery the aim is to demonstrate to what extent the occurrence and severity of delirium can be predicted at the time of surgery (‘intraoperatively’).

The recording of raw EEG data will be made on routinely available anaesthetic monitors that are available in clinical practice for the monitoring of depth of anaesthesia. The recording will be continuous frontal montage raw EEG, to commence at the start of anaesthesia until the end of surgery with analysis retrospectively. The recordings will be downloaded from the EEG monitor at the recruitment centre after the operation according to relevant recruitment centre SOPs or policies. The download of the digital recording will be sent to the University of Oxford via a secure server that each recruitment centre participating in the mechanistic work will be given upload access to. The recordings will be stored on secure servers at the University of Oxford. Analysis of the patterns of EEG will take place at the University of Oxford with the comparison identification number as the identifier.

The anaesthetist caring for the participant will not be required to make any interpretation of the raw EEG during surgery – this data will be analysed retrospectively when paired with the markers of neuronal inflammation.

4.7 Definition of End of Comparison

The end of the comparison is the point at which the follow up of the last participant has been completed, all the data has been entered and all queries have been resolved. The last direct data collection will be at

one year post-diagnosis of a hip fracture of the last participant. The Sponsor, MHRA and main REC will be notified in writing if the comparison has been concluded or terminated early.

5 INTERVENTIONS

5.1 Description of the randomised treatments

Participants will be randomly allocated to one of the treatment arms:

- Intervention: Single infusion of infliximab at 5mg/kg body weight, diluted in 250ml of 0.9% saline and administered intravenously over a 2-hour period
- Placebo control: Identical volumes of 0.9% saline

Both infliximab and saline have marketing authorisation and infliximab is approved for use at the dose that will be administered in accordance with this protocol appendix, but outside its licensed indication. They will both be prepared as per section 10.1.1 below prior to administration.

All recruitment centres will be required to use Infliximab 100 mg powder concentrate for reconstitution in solution for infusion. It will be supplied by the manufacturer or their agents to the recruitment centres.

10.1.1 Labelling, Storage and Administration of the IMP

A batch of the IMP will be ring-fenced for the comparison and stored in the operating theatre in accordance with the requirements as described in the approved SmPC. This box will be labelled by pharmacy with a comparison-specific annex 13 compliant clinical trial label on its outer packaging (label A).

A comparison-specific prescription will be prepared by a delegated member of staff. An appropriately trained clinician not involved in the assessment of any comparison outcomes will carry out the online treatment allocation reveal process. The medication will be prepared following local processes for the reconstitution of monoclonal antibodies.

The infusion will be prepared in an area away from any blinded members of the clinical team so as not to reveal the treatment allocation to potential blinded assessors. The infusion bag will be labelled as per routine clinical practice in the operating theatre, indicating the bag contains either the IMP or placebo (Label B). The IMP and placebo are clear colourless solutions, indistinguishable to the human eye. No members of the blinded assessment staff will be present in the operating theatre.

The medication will then be administered by the attending anaesthetist within 24 hours of reconstitution. The name of the person administering the trial treatment will be recorded on the treatment CRF. The attending anaesthetist will give the intravenous intervention or placebo over a 2-hour period. It is standard practice for anaesthetists to follow instructions on how to draw up and administer drugs during surgery. In addition, it is standard UK practice to affix pre-printed labels to drugs used by anaesthetists. The label that will be affixed to the infusion bag is not classed as a trial specific labelling, simply a standard of care.

10.1.2 Accountability of the Comparison Treatment

As this is a pragmatic comparison involving a one-off administration of the intervention, a risk adapted approach has been employed to ensure the appropriate level of documentation is kept to record IMP accountability as per standard local practice. For clarity - pharmacy involvement is limited to taking receipt of the IMP from the supplier and the initial labelling of the bulk batch. Drug accountability logs will be kept

with the IMP and completed by a trained and unblinded (i.e. not involved in the assessment of any comparison outcomes) member of staff as per the delegation log. Number of packs stored in the operating theatre and batch numbers for each box will be recorded. Participants' weight will also be documented here to ensure that the correct amount of drug is prepared.

10.1.3. Anaesthetic technique

A regional or general anaesthesia technique will be used for each participant as per routine clinical care. Intra-operative analgesia may be achieved by combining a local anaesthetic nerve block, plus paracetamol 1g and opioid analgesia as clinically indicated. Surgery to fix or replace the broken part of the hip will take place using the preferred technique and implants of the operating surgeons as per routine clinical practice. Relevant details of the treatment pathway will be recorded.

10.1.4 Safety of the IMP

Anti-TNF agents act by binding to circulating TNF released by the trauma associated with injury and surgery and the complexes are rapidly cleared by the mononuclear phagocyte system. Infliximab is the only anti-TNF approved for IV administration (infusion over 2 hours). This method of delivery will ensure that peak levels are present in the circulation for the entire duration of the surgery and in the immediate post-operative period. More than 20 million patients have been treated with the anti-TNFs and over 3 million with infliximab. The drug has an exceptional safety record. An early Cochrane review[39] found no increase in adverse events in patients with rheumatoid arthritis treated with infliximab compared to placebo. A more recent systematic review of elderly patients with psoriasis identified increased infusion related reactions, reactivation of TB and chest infections[40]. A meta-analysis of adverse events in patients with rheumatoid arthritis treated with infliximab confirmed that there were more infusion related reactions but no significant risk of infection compared to placebo.[41] The Food and Drug Administration report of increased respiratory and genito-urinary infections has been noted, as well as reactivation of latent TB. However, it is important to note that all these data pertain to patients receiving regular anti-TNF over a period of many years whilst this protocol appendix only calls for administering a single dose. Early trials of Infliximab for inflammatory bowel disease in patients receiving repeated doses had uncertainty regarding an association with lifetime risk of malignancy. However, in this study we will only be administering infliximab on a single occasion and large scale registry data demonstrated infliximab is not related to increased risk of malignancy[42].

10.1.7 Concomitant Medications

Section 4.5 of the Summary of Product Characteristics should be referred to for concomitant medications to avoid prior to and during dosing with infliximab.

10.7.8 Post trial care

No post-trial care is relevant to this randomised comparison. Participants will receive standard of care given to all patients with a hip fracture. There will be no provision of the IMP after the end of the comparison.

6 SAFETY REPORTING

Safety reporting for each participant will begin from the time of consent and will end when the participant has reached their final follow up time point, at 1 year post-diagnosis of a hip fracture. As the safety profile

of Infliximab is very well known, only SAEs will be reported for this comparison. Investigators should follow up serious adverse events until resolved or until stabilisation or resolution.

All SUSARs are to be reported according to the guidelines relevant to CTIMPs specified in the Platform Master Protocol.

6.1 Related and expected Serious Adverse Events

See Platform Master Protocol for details of SAEs that are expected and related to the fracture and surgical procedure. Additional expected and related SAEs, which in line with the Platform Master Protocol are reported using a complications form, for this comparison are:

- Reactivation of TB is an expected event that is associated with the IMP, including a positive result from the peri-operative ELISpot tests.

6.2 Expectedness

See Platform Master Protocol detail on the assessment of expectedness. For SAEs that require reporting, expectedness of SARs will be determined according to the relevant RSI section of the Summary of Product Characteristics. The RSI used (within the SmPC) will be the current Sponsor and MHRA approved version at the time of the event occurrence. All SARs which are more specific or more severe in nature or present as a life-threatening event will be reported as SUSARs.

7 STATISTICS & ANALYSES

7.1 Sample Size Determination

The proposed sample size for this study is 564 participants. The Minimal Clinically Important Difference for the MDAS is 2.5 on the 0-30 point scale. Prior estimates of the Standard Deviation of the peak MDAS in the post-operative period in patients with hip fracture was 7.0[4]. However in an recent NIHR-funded feasibility comparison nested within the WHiTE platform, the standard deviation of peak MDAS was estimated to be 8.4. This equates to a small to moderate effect size of 0.30. A sample size of 478 participants (239 per arm) will enable the detection of an effect size of 0.30 based on a null hypothesis of no difference with 90% power and 5% (2-sided) significance. Allowing for 15% loss to follow-up, this is inflated to 564 patients (282 per arm). Although we do not anticipate this level of attrition for the primary outcome measure, this inflation of the sample size calculation will allow us to collect high-quality secondary outcome data.

It is anticipated that the DSMC will review the sample size assumptions. In particular, the standard deviation and the distribution of the peak MDAS, will be reviewed at the end of the internal pilot phase of the comparison and again when approximately half of the participants have reached their primary outcome time-point.

Due to the exploratory nature of the mechanistic objectives, no sample size calculation has been conducted. Data will be collected during the internal pilot phase. Analysis will be performed on all available samples and will provide important data to allow for further grant funding to be obtained.

7.2 Analysis Populations

The primary analysis population will be intention to treat (ITT); that is all participants will be analysed as randomised. Sensitivity analyses will be undertaken on the per-protocol population for the primary outcome and key secondary outcomes.

The ITT population includes all randomised participants including:

1. Participants who are randomised but do not undergo surgery (such as those who died or were found to be ineligible after randomisation but before surgery).
2. Participants who are randomised and found to be ineligible during or after surgery.

Note: participants who withdraw from the comparison between randomisation and 1 year post-diagnosis of a hip fracture will provide data up to the point of withdrawal.

The 'PP' population will be the ITT population excluding participants as described in 1 and 2 above and other major deviations from the protocol which will be fully described in the Statistical Analysis Plan.

7.3 The Level of Statistical Significance

The statistical significance will be assessed at 5% for two-sided tests. All p-values will be reported to 3 decimal places. 95% confidence intervals will be reported throughout.

7.4 Decision Points

We will exploit the efficiencies available from nesting this comparison within the Platform. This Platform has been built based upon the experiences of the WHiTE cohort study which has successfully delivered six hip fracture trials. The comparison processes are streamlined and harmonised with those of the Platform so that we should be able to achieve 65% recruitment of eligible patients and 90% follow-up of available participants (those alive and not withdrawn) at the primary outcome time-point.

During the internal pilot phase, we expect to recruit 120 patients from 4 pilot recruitment centres. The DSMC and POC will closely monitor recruitment during the feasibility phase and make a recommendation with regards continued progress of the comparison. If recruitment is below 70 participants, we will consider stopping the comparison for feasibility reasons. If between 70 and 100 participants, we will review the recruitment processes and implement the committees' recommendations. If recruitment is more than 100 participants, we will progress with the main phase of the study. A total of 564 participants will be randomised across approximately 8 recruitment centres. In the event that recruitment in each of the centres is lower than anticipated we have a network of 120 hospitals in addition to the proposed 8 centres that have previously worked with us on multicentre trials.

It is anticipated that the DSMC will assess the sample size assumptions both at the end of the internal pilot phase, and after about 50% of the participants have been randomised.

7.5 Analysis

A full, detailed SAP will be drafted early in the comparison, and will be finalised prior to the primary analysis data lock. Any subsequent changes to the SAP will be fully justified in the final report. Stata (StataCorp LO) or another appropriate validated statistical software will be used for analysis.

If the trial stops early, due to being non-feasible or for any other reason, the study will be analysed and reported as an external pilot/feasibility study.

Otherwise, patients from the internal pilot/feasibility stage will be included in the final analysis and the study reported as per the CONSORT statement and any relevant extensions. Baseline demographic data will be summarised by treatment groups to assess comparability between treatment arms. Binary and categorical data will be summarised as frequencies and percentages, normally distributed continuous data will be summarised as means and standard deviations, and non-normally distributed continuous data as medians and interquartile ranges. Primary and secondary outcomes will be explored graphically.

The main analysis will investigate differences in the primary outcome measure, the peak (maximum) MDAS scores during the first five days post-operatively, which will be fully described in the Statistical Analysis Plan. The principal analyses will be conducted on the ITT population using a mixed-effects linear regression model adjusting for stratification factors. Centre will be included as a random effect to allow for any heterogeneity in response between centres, and the presence or absence of permanent cognitive impairment pre-surgery included as a fixed effect. Models will also adjust for important baseline covariates as fixed effects to maximise precision, which will include age as a continuous variable, sex, type of surgery as either fixation or total hip replacement, and type of anaesthesia as either general anaesthetic or spinal anaesthetic. The treatment difference will be based on the estimate of adjusted means and 95% confidence intervals, with a 2-sided significance level of 5% being used for comparative tests. The sensitivity of the primary outcome data to the underlying population will be assessed using the PP population; the definitions of this population are described in section 12.2 and will be fully defined in the SAP.

The analysis of secondary clinical outcomes will use multi-level mixed effects regression models and will include all time-points, where appropriate. Continuous outcomes will be analysed using linear mixed effects regression, and binary outcomes will be analysed using logistic mixed effects regression.

Missing data will be minimised through careful data management. Missing data will be described with reasons given where available; the number and percentage of individuals in the missing data category will be presented by treatment groups. The nature and mechanism for missing variables and outcomes will be investigated and sensitivity analyses will be undertaken to assess the underlying missing data assumptions, in particular whether it can be treated as *missing completely at random*. Missing data may be imputed in sensitivity analyses if considered beneficial to the interpretation of the main findings. Any imputation methods used for scores and other derived variables will be carefully considered and justified. Reasons for ineligibility, non-compliance, withdrawal or other protocol violations will be stated and any missing data patterns summarised.

Serious adverse events will be explored to assess if they differ between groups.

A detailed description of the analysis of the exploratory mechanistic outcomes will be included in the SAP.

8 DISSEMINATION POLICY

Outputs with regards the primary objective of this comparison will be submitted for publication within 12 months of the end of comparison. Further outputs will be expected within 5 years of the end of comparison.

Comparison summaries will be provided to clinicians through the network of WHiTE investigators and presented at local and regional multidisciplinary meetings. In addition, we will produce:

- Plain English outputs, led by the UK Musculoskeletal Trauma Public and Patient Involvement group and distributed via paper, web and blog media
- Major international free-to-access publications including the protocol and Statistical Analysis Plan, as well as the main trial results
- National presentations – Orthopaedic Trauma Society, Age Anaesthesia & British Geriatrics Society
- International presentations – Global Fragility Fracture Network Congress, International Orthopaedic Trauma Association Congress.

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Inclusion Criteria

1. Patient's age 60 years old and over
2. Patient is diagnosed with a hip fracture that in the opinion of the treating surgeon may benefit from surgical treatment

10 ANNEX A: FLOW CHART

Exclusion Criteria

1. The patient has severely impaired renal function eGFR <30 ml.min-1
2. The patient has severely impaired hepatic function
3. The patient is currently taking any anti-TNF drug
4. The patient has a contra-indication to anti TNF injection
5. The patient has a known hypersensitivity to any anti-TNF agent or any of the excipients
6. The patient has known active tuberculosis (TB) or history of TB or at risk of developing TB e.g., through the use of immunosuppressants
7. The patient has another known active infection (chronic or localised) or known history of recurring infections or condition which may predispose patients to infection, including the use of concomitant immunosuppressive medications
8. The participant has known lung fibrosis.
9. The patient had systemic inflammatory disorder such as rheumatoid arthritis or inflammatory bowel disease
10. The patient has known moderate to severe heart failure (NYHA class III/IV)
11. The patient has HIV, Hepatitis B or C (based on medical history)
12. The patient is at risk of Hepatitis B or HIV infections, including intravenous drug use
13. The patient has been diagnosed with Multiple Sclerosis (MS) or other central or peripheral nervous system demyelinating disorders
14. History of malignancy within five years prior to screening or any evidence of persistent malignancy, except basal cell or squamous cell carcinomas of the skin, or cervical carcinoma in situ which has been treated or excised in a curative procedure.
15. The patient has had a live vaccination 4 weeks prior to study entry or will require one within 12 weeks after the study intervention
16. The patient takes biologics including anakinra or abatacept or DMARDS
17. The patient is or has been participant in a clinical trial of a medicinal product in the last 12 weeks
18. Previous participation in the same randomised comparison
19. A second hip fracture (other side) while the patient is still enrolled in the Platform following their first fracture