World Hip Trauma Evaluation Appendix 13 – Delirium and Cognitive Impairment (DeCI) Statistical Analysis Plan

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1. INTRODUCTION

This document details the proposed data presentation and analysis for the main paper(s) and final study reports from the ***NIHR & Cannbiorex Pharma LTD funded, multicentre, two-arm, randomised, placebo-controlled superiority comparison assessing the effect of infliximab on delirium following hip fracture surgery (WHiTE13-DeCI)***. The results reported in these papers should follow the strategy set out here. Subsequent analyses of a more exploratory nature or of extended study follow-up will not be bound by this strategy unless explicitly stated to be covered, though they are expected to follow the broad principles laid down here. The principles are not intended to curtail exploratory analysis (for example, to decide cut-points for categorisation of continuous variables), nor to prohibit accepted practices (for example, data transformation prior to analysis), but they are intended to establish the rules that will be followed, as closely as possible, when analysing and reporting the trial. This document follows published guidelines regarding the content of statistical analysis plans for clinical trial (1).

The analysis strategy will be available on request when the principal papers are submitted for publication in a journal. Suggestions for subsequent analyses by journal editors or referees, will be considered carefully, and carried out as far as possible in line with the principles of this analysis strategy. If reported, the analyses will be marked as post-hoc; the source of the suggestion will be acknowledged, and the reader will be advised to rely primarily on the pre-specified analysis for the interpretation of the results.

Any deviations from the statistical analysis plan will be described and justified in the final report of the trial. The analysis should be carried out by an identified, appropriately qualified and trained statistician, who should ensure the integrity of the data during their processing. Examples of such procedures include quality control and evaluation procedures.

Integral to this Statistical Analysis Plan (SAP) is the SAP – Data Definitions and Tables document which will include full detailed descriptions of all key outcomes, including their definition, generation and how they will be reported at the end of the study. These two documents should be read in tandem.

1.1 Key personnel

List of key people involved in the drafting and reviewing this SAP, together with their role in the trial and their contact details.

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1.2 Changes from previous version of SAP

A summary of key changes from earlier versions of SAP, with particular relevance to protocol changes that have an impact on the design, definition, sample size, data quality/collection and analysis of the outcomes is provided below.

Version number Issue date	Author of this issue	Protocol Version & Issue date	Significant changes from previous version together with reasons
V1.0_02Mar2026	Fema Er	WHiTE Platform Protocol_V8.0_08Nov2024 WHiTE13-DECI Protocol_V4.0_24Mar2025	Not applicable as this is the 1st issue

2. BACKGROUND AND OBJECTIVES

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 (2). One quarter of all patients with hip fracture suffer with post-operative delirium (3). 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. 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, increased mortality and long-term cognitive impairment (4–7). The aim of this trial is to 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.

The trial consists of two phases. Phase 1 (internal pilot) is the period during which the first 120 consecutive participants are consented into the study, with the intent to proceed to the definitive trial if feasibility is demonstrated. Phase 2 (main phase) extends the randomised comparison, in which the remainder of the 564 participants are recruited.

Due to difficulties with recruitment, the trial did not progress to the main phase. The SAP has therefore been revised to report only the feasibility part of the trial.

The **primary objective** is to compare peak delirium in the 5 days following hip fracture surgery between the treatment groups.

Secondary objectives are to compare the following between the treatment groups:

- Cognitive impairment scores at 4 and 12 months post-diagnosis of a hip fracture
- Health-related quality of life at 4* and 12 months post-diagnosis of a hip fracture
- Mortality risk within first 12 months post-diagnosis of a hip fracture
- Mobility at 4* and 12 months post-diagnosis
- Residential status at 4 *and 12 months post-diagnosis of a hip fracture
- Risk and pattern of complications at any point within the first 12 months post-diagnosis of a hip fracture
- Healthcare and broader resource implications

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

Exploratory mechanistic objectives:

The protocol describes also exploratory mechanistic objective i), ii) and iii) as described below and they are part of a separately funded sub-study. All three objectives are not part of this SAP. Exploratory mechanistic objective i) will be described in a separate appendix to this SAP. Objectives ii) and iii) are part of a separate DPhil project and therefore will be described and reported elsewhere.

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 estimand for the primary objective (including the analysis of the primary outcome) is described in **Table 1**.

Table 1: Estimand-to-analysis table

Primary Objective: To compare peak delirium in the 5 days following hip fracture surgery between the treatment groups	
Estimand: The mean difference in peak MDAS score during the first five post-operative days between adults aged 60 years and over with a hip fracture randomised to receive infliximab and randomised to receive placebo.	
Treatment: Single infusion of infliximab at 5mg/kg body weight, diluted in 250ml of 0.9% saline and administered intravenously over a 2-hour period	
Estimand	***Analysis***
Target population Adults aged 60 years and over with a hip fracture, who in the opinion of the treating surgeon may benefit from surgical treatment.	***Analysis set*** As randomised (intention-to-treat (ITT)) population, including all randomised participants with available outcome data in their allocated groups, irrespective of compliance with the protocol and post-randomisation events.
Outcome Peak Memorial Delerium Assessment Scale (MDAS) score. Peak MDAS is the highest of at least 2 available scores over the first five days post-surgery.	***Outcome definition*** 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. Peak MDAS is the highest of at least 2 available scores over the 5 days. Participants need to provide at least 2 scores for the MDAS peak to be obtained.
Handling of intercurrent events Post-randomisation events which may affect the interpretation or existence of the primary outcome measure include: - Not undergoing surgery. - Death. - Not receiving allocated treatment. All intercurrent events will be addressed using a treatment policy strategy, i.e. data from participants who experience an intercurrent event will be included in the analysis under the treatment group they were randomise to.	***Handling of missing data*** Primary outcome will be analysed using all available data.
Population-level summary measure	***Analysis approach***

Mean difference in peak MDAS during the first 5 days post-operatively between intervention and control groups.	Linear regression model adjusting for stratification factors (presence of cognitive impairment at randomisation at a minimum and site if possible) and age and sex if possible. Sensitivity analyses: Will explore the impact of the minimum number of MDAS measurements required to obtain a peak value (see Section 0).

3. STUDY METHODS

3.1 Trial Design/framework

WHiTE13-DECI is a multi-centre, two-arm, placebo-controlled, superiority randomised comparison embedded within the overarching WHiTE Platform. It is a two-phased comparison. Phase 1 (internal pilot) is the period during which the first 120 consecutive participants are consented into the study, with the intent to proceed to the definitive trial if feasibility is demonstrated. Phase 2 (main phase) will extend the randomised comparison, in which the remainder of the 564 participants will be recruited.

Feasibility was not demonstrated during the internal pilot phase. The trial did not progress to the main phase. The SAP has therefore been revised to report the feasibility part of the trial only.

3.2 Randomisation and Blinding

Randomisation was on a 1:1 basis to infliximab or placebo, stratified by recruitment centre and the presence/absence of cognitive impairment at presentation using stratified block randomisation. The allocation sequence was generated by the trial statistician using variable block sizes.

Full details of the randomisation are available in WHiTE13-DECI_RBP_V2.0_09Apr2024, stored in the confidential statistical section of the TMF.

This is a double-blinded comparison, whereby the participant and the local research team members involved in the delirium assessment and data collection process are blinded to the allocated treatment. No formal assessment of the success or otherwise of the blinding will be made. Any unblinding will be documented at the end of the comparison in the statistical report.

3.3 Sample Size

The original proposed sample size for this study was 416 participants. The minimal clinically important difference for the MDAS is 2.5 on the 0-30 scale and, in patients with hip fracture, the standard deviation (SD) for the peak MDAS in the post-operative period is 7.0 (5). This equates to a moderate effect size of 0.36. A sample size of 332 participants (166 per arm) would enable the detection of an effect size of 0.36 based on a null hypothesis of no difference with 90% power and 5% (2-sided) significance. Allowing for 20% loss to follow-up, this was inflated to 416 patients (208 per arm). Although this level of attrition for the primary outcome measure was not anticipated, this inflation of the sample size calculation would allow us to collect high-quality secondary outcome data.

However, in a recent NIHR-funded feasibility comparison nested within the WHiTE platform, the SD of peak MDAS was estimated to be 8.4. This equates to a small to moderate effect size of 0.30. The sample size calculation was updated based on this SD, resulting in a new sample size of 478 participants (239 per arm) to 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 a realistic 15% loss to follow-up, this was inflated to 564 (282 per arm).

It was anticipated that the Data Safety Monitoring Committee (DSMC) would review the sample size assumptions, in particular the SD and distribution of peak MDAS, at the end of the internal pilot phase and again when approximately half of the participants reached their primary outcome timepoint. This review did not happen as the trial stopped recruitment early.

An independent check of the sample size is stored in the statistical TMF (DECI_SampleSizeVerification_14Dec2023).

3.4 Statistical Interim Analysis, Data Review and Stopping guidelines

A Data Safety Monitoring Committee (DSMC) has been appointed for the WHiTE Platform and follows the charter as described in the document WHiTEPlatform_DSMCCharter_V2.0_18Dec2023, stored in the TMF. DSMC meetings are held at least annually during which the committee reviews all active comparisons on the WHiTE Platform. One DSMC meeting was held for WHiTE13-DECI before its early closure.

No formal interim analyses were planned.

3.5 Timing of Analysis

The final analysis of the primary and all secondary endpoints up to 4 months will be conducted as soon as possible following the early closure of the trial and sufficient time has been allowed for data collection and cleaning. Secondary outcomes at the 12-month timepoint will be analysed at the end of the 12 months follow-up and will be reported elsewhere.

3.6 Blinded analysis

No blinded analysis will be done given the study has closed early.

3.7 Statistical Analysis Outline

All principal analyses will be based on the intention-to-treat (ITT) principle (“as randomised”), analysing participants in the groups to which they are randomised, irrespective of compliance with the treatment allocation.

The primary outcome (post-operative delirium measured by the Memorial Delerium Assessment Scale (MDAS)) will be summarised descriptively by treatment arm, using means with SDs and medians with IQRs. A linear regression model of peak MDAS versus treatment, adjusting for stratification factors (presence of cognitive impairment at randomisation at a minimum and site if possible) and also age and sex, if possible, will be fitted. Two-sided 5% significance will be used and 95% confidence intervals with associated p-value will be reported. The primary analysis will be repeated on the per-protocol population.

Secondary outcomes will be reported descriptively by treatment arm, using means with SDs and medians with IQRs for continuous outcomes and numbers with percentages for categorical outcomes.

Due to difficulties with recruitment, the trial did not progress to the main phase. The SAP has therefore been revised and differs from the statistical analysis outlined in the protocol. Mixed effects models described in the protocol for primary and secondary outcomes will not be conducted. Secondary outcome sensitivity analyses and primary outcome missing data sensitivity analyses will also not be conducted.

4. STATISTICAL PRINCIPLES

4.1 Statistical Significance and Multiple Testing

No formal adjustment for multiple significance testing is intended, as only a single primary outcome is considered. Therefore, significance levels used will be 5% and 95% confidence intervals will be reported. Secondary outcomes will also be analysed using a significance level of 5% and 95% confidence intervals.

4.2 Definition of Analysis Sets

Intention-to-treat (ITT) population includes all randomised participants, analysed as they were randomised, irrespective of the treatment they actually received, 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.

Per-protocol (PP) population is the ITT population as above, excluding participants described in 1 and 2 and also excluding participants with protocol deviations deemed as important.

5. TRIAL POPULATION AND DESCRIPTIVE ANALYSES

Descriptive analysis will include summary of flow of trial participants through the trial and baseline stratification, demographic and clinical characteristics of each group.

5.1 Representativeness of Study Sample and Patient Throughput

The flow of participants through each stage of the trial, including numbers of participants randomly assigned, receiving intended treatment or otherwise, and analysed for the primary outcome will be provided and presented using a CONSORT 2025 flow diagram (8) as outlined in **Figure 1**. Information relating to the screening data including the number of patients screened, agreed or declined to participate, ineligible patients randomised or randomisation conducted in error will be summarised.

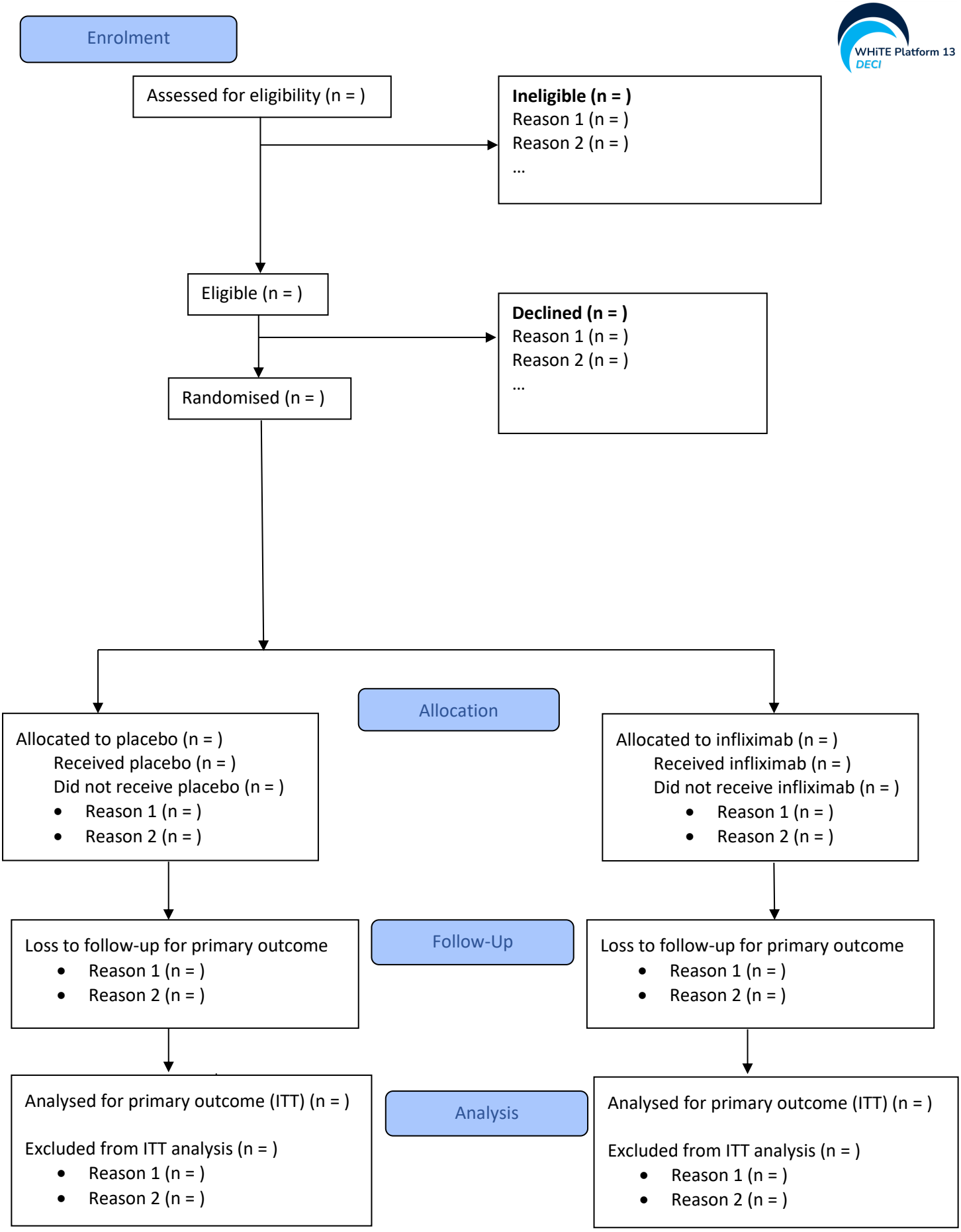


Figure 1: CONSORT Flow Diagram

5.2 Withdrawal from treatment and/or follow-up

The numbers (with percentages) of participants who withdraw during the trial follow-up will be reported by treatment group together with reasons for withdrawal where available. Details on whether or not primary outcome data is available for those who withdraw will be summarised.

5.3 Baseline Characteristics

Baseline characteristics will be reported by treatment group, including the stratification factors and important prognostic, demographic and clinical covariates.

Numbers (with percentages) for binary and categorical variables and mean (and standard deviation), or median (with lower and upper quartiles) for continuous variables will be presented; there will be no tests of statistical significance nor confidence intervals for differences between randomised groups on any baseline variable.

Details of how the baseline data will be displayed are described in SAP - Data Definitions and Tables documents:

- WHiTEPlatform_SAP_DD&T_V1.3_24Feb2026

  Table WP-1: Continuous baseline characteristics by treatment group
  Table WP-2: Baseline characteristics (Baseline Participant CRF) by treatment group
  Table WP-3: Baseline characteristics (Baseline Hospital CRF) by treatment group

- WHiTE13-DECI_SAP_DD&T_V2.0_02Mar2026

  Table DECI-1: Stratification factors by allocated treatment group

5.4 Unblinding

All cases of unblinding will be listed, together with who was unblinded, reasons for unblinding and summarised (numbers, percentages).

5.5 Treatment Compliance with Details of Intervention

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: Identical volumes of 0.9% saline.

Compliance with the intervention will be summarised by treatment group, along with reasons participants did not receive their allocated intervention, as in Table DECI-2 in WHiTE13-DECI_SAP_DD&T_V2.0_02Mar2026.

5.6 Reliability

Prior to analysis, validation checks of the data will be conducted. This will include checking for duplicate records and ensuring data are of the appropriate format, for example within the maximum possible range of values. Clarification will be sought by the trial office in the case of discrepancies.

Data validation checks will also be performed in order to check calculations and processes performed by a computer program. This will include checking if data have been imported and merged correctly.

6. ANALYSIS

The statistical methods to be used to compare groups for primary and secondary outcomes and methods for point and interval estimation are summarised below.

6.1 Outcome Definitions

Primary Outcome

The primary outcome is the peak post-operative delirium measured by the Memorial Delerium Assessment Scale (MDAS) (9). The MDAS is a validated scale which quantifies the severity of delirium based on 10 features which integrates behavioural observations with objective cognitive testing (10). The 10 features are: 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. MDAS generates a scale from 0 to 30, with 30 being the most severe delirium. 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. Peak delirium will be compared between the treatment groups.

MDAS is collected daily during the first five days post-surgery. Peak MDAS is the highest of at least 2 available scores over the 5 days. Participants need to provide at least 2 scores for the MDAS peak to be obtained.

Secondary Outcomes

- Cognitive impairment scores (Telephone Interview for Cognitive Status (TICS) (11) measured at 4 and 12 months post-diagnosis of hip fracture.

  TICS is a standardised test of cognitive functioning that can be administered over the telephone. It consists of 11 items. The total score ranges from 0 to 41, with higher scores indicating better outcome.

- Health related quality of life (EQ-5D-5L index and EQ VAS) measured at 4 and 12 months post-diagnosis of hip fracture.

  The EQ-5D-5L index is a validated measure of health-related quality of life (12), consisting of a five-dimension health status classification system and a separate visual analogue scale. It can be completed by patient or proxy, where the patients are unable to self-report. EQ-5D-5L index scores range from -0.594, indicating the worst possible health state, to 1, indicating full health. A score of 0 represents a health state equivalent to death. A score of 0 is imputed for participants who have died by the post-randomisation timepoint.

- Mobility (Modified New Mobility Score (mNMS) (13) measured at baseline and 4 and 12 months post-diagnosis of a hip fracture.

  The mNMS is a multi-component instrument that assesses ambulation inside the home, outside the home and whilst shopping. Total score ranges from 0 (no walking ability at all) to 9 (fully independent).

- Residential status (UK National Hip Fracture Database (NHFD) Residential Status) measured baseline and 4 and 12 months post-diagnosis of a hip fracture.

  Changes in residential status provide a marker for the patients' independence through their hip fracture recovery. It is reported by participants or their proxy using an ordinal scale as per the NHFD: (1) own home/sheltered housing, (2) residential care, (3) nursing care, (4) rehabilitation unit – hospital bed in the current trust, (5) rehabilitation unit – hospital bed in another trust, (6) rehabilitation unit – NHS funded care home bed, and (7) acute hospital.

- Risk and pattern of complications at any point within the first 12 months post-diagnosis of a hip fracture.

All expected serious adverse events related to the fracture and standard surgical procedure are recorded as complications (collected on the Complications Form), unless they are more severe than expected in which case, they are reportable SAEs. In addition to the Platform complications, additional expected and related SAEs for WHiTE13-DECI are reported using a complications form - DECI Tuberculosis Form. Reactivation of tuberculosis (TB) is an expected event that is associated with the IMP, including a positive result from an ELISpot test.

- Mortality risk measured up to 12 months post-diagnosis of a hip fracture.

Details on how these outcome variables will be generated and reported are provided in WHiTE13-DECI_SAP_DD&T_V2.0_02Mar2026.

6.2 Analysis Methods

Primary outcome

The main analysis will investigate differences in the primary outcome measure, the peak (maximum) MDAS scores during the first five days post-operatively. Participants need to provide at least two measurements over the five days for a peak MDAS to be obtained. The number of MDAS measurements provided by participants will be summarised by treatment group using means and standard deviations (SD) or medians and inter-quartile ranges (IQR) as appropriate. The number and percentage of participants who provided two or more MDAS scores will also be reported.

Peak MDAS will be presented descriptively by treatment group using means and SDs and medians and IQRs. These summaries will be produced for the ITT population using available cases.

A linear regression model adjusting for stratification factors (presence of cognitive impairment at randomisation at a minimum and site if possible) and also age and sex, if possible, will be conducted on the ITT population to estimate a treatment effect.

Secondary outcomes

All secondary outcome summaries and tests will be conducted on the ITT population using available cases. Descriptive statistics will be presented without any statistical inference.

Continuous outcomes (TICS, EQ-5D-5L index scores, EQ VAS and mNMS) will be presented descriptively by treatment group using means and SD and medians and IQR at each timepoint. No statistical inference will be conducted.

Additionally, TICS total score can be categorised into four groups (14): 33-41 nonimpaired, 26-32 ambiguous, 21-25 mildly impaired and ≤20 moderately to severely impaired. The numbers and percentages by treatment group will be summarised at each timepoint for these categories.

Categorical outcomes (residential status) will be summarised at each timepoint by treatment group using numbers and percentages. No statistical analysis will be performed.

The number and percentage of participants reporting each type of complication will be summarised by treatment group. The number and percentage of participants reporting at least one complication will be summarised by treatment group. The number of complications reported per participant will also be summarised using numbers and percentages by treatment group.

The number of deaths will be summarised by treatment group. Days from randomisation to death will be summarised by treatment group using means and SDs and medians and IQRs.

6.3 Missing Data

Missing data will be summarised by treatment arm.

6.4 Sensitivity Analysis

A sensitivity analysis will be conducted to assess the impact of the minimum number of MDAS measurements required to obtain a peak value. The primary outcome analysis will be repeated for peak MDAS defined as the highest of at least one available score and also for peak MDAS defined as the highest of at least three available scores.

No further sensitivity analyses are planned.

6.5 Pre-specified Subgroup Analysis

No subgroup analyses are planned.

6.6 Supplementary/ Additional Analyses and Outcomes

There will be no additional analyses for the primary and secondary outcomes as only descriptive statistics and inferences conducted by a linear regression model will be reported.

6.7 Harms

The total number of SAEs, the number of participants with at least one SAE and the number of SAEs per participant will be summarised by allocated treatment arm. A line listing of SAEs will also be given, providing details on the SAE, allocated treatment, treatment received, days since randomisation, reason for seriousness, causality and expectedness

6.8 Health Economics and Cost Effectiveness (where applicable)

A Health economic analysis is planned and the details are summarised in the protocol (WHiTE13_DECI_ProtocolAppendix_V4.0_24Mar2025). These are analyses are beyond the scope of this SAP and are detailed elsewhere.

7. VALIDATION OF THE PRIMARY ANALYSIS

To validate the primary outcome a statistician not involved in the trial analysis will independently repeat the analyses detailed in this SAP. This may be by using different statistical software. The results will be compared and any unresolved discrepancies will be reported in the Statistical report (See OCTRU SOP: STATS-005 Statistical Report).

8. SPECIFICATION OF STATISTICAL PACKAGES

All analysis will be carried out using appropriate validated statistical software such as STATA, or R. The relevant package(s) and version number(s) will be recorded in the Statistical report.

9. PUBLICATION

This study will be/has been conducted as part of the portfolio of trials in the registered UKCRC Oxford Clinical Trials Research Unit (OCTRU) at the University of Oxford. It will follow/has followed their Standard Operating Procedures ensuring compliance with the principles of Good Clinical Practice and the Declaration of Helsinki and any applicable regulatory requirements.

10. REFERENCES

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APPENDIX: GLOSSARY OF ABBREVIATIONS

CI	Chief Investigator
CSM	Centre for Statistics in Medicine
DSMC	Data and Safety Monitoring Committee
EQ-5D-5L	EuroQol 5 Dimensions 5 Levels
EQ VAS	EuroQol Visual Analogue Scale
HEAP	Health Economic Analysis Plan
ICE	Intercurrent Event
IQR	Interquartile Range
ITT	Intention-To-Treat
MDAS	Memorial Delerium Assessment Scale

mNMS	Modified New Mobility Score
NHFD	National Hip Fracture Database
NIHR	National Institute for Health and Care Research
OCTRU	Oxford Clinical Trials Research Unit
SAP	Statistical Analysis Plan
SD	Standard Deviation
TICS	Telephone Interview for Cognitive Status
TSC	Trial Steering Committee