APPENDIX 16 to WHiTE Platform Master Protocol

World Hip Trauma Evaluation 16

A pilot randomised trial of Delirium prevention in Fragility Hip Fractures with Corticosteroids (DelPHiC)

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.

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World Hip Trauma Evaluation Appendix 16 – DELPHIC: A pilot randomised trial of Delirium prevention in Fragility Hip Fractures with Corticosteroids

Short title: WHiTE 16- DELPHIC

Date and Version No: V2.0 11Sep2025

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We declare no conflicts of interest.

Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, HRA, host organisation, and members of the Research Ethics Committee and Regulatory Authorities unless authorised to do so.

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1 APPENDIX AMENDMENT HISTORY

Amendment No.	Protocol Appendix Version No.	Date issued	Author(s) of changes	Details of Changes made
AM27 (Resubmission in response to MHRA Non-Acceptance of initial submission)	2.0	11Sep2025	Amrita Athwal	9.1.3: Update to add additional exclusion criteria (5-13) to eligibility section in response to MHRA non acceptance of amendment 10.1.6: Addition of reference to section 4.4 of SmPC to refer to concomitant medications; in particular referring to the receipt of live vaccines 15: Annexe 1 Flow chart updated with additional exclusion criteria

2 KEY CONTACTS

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3 LAY SUMMARY

Breaking your hip is a bad injury that can happen when you trip or fall. It needs an operation to fix it, and then it takes a long time to get better. Sadly, about one in four people who break their hip die within a year, and those who live often have a reduced quality of life. In the UK around 75,000 people break their hip each year, and over a million across the world.

Some people who have an operation to fix their broken hip get a condition called delirium. This makes them confused and unable to think clearly. Delirium is often very frightening. Even though most people with delirium get better, it makes their stay in the hospital longer and can make them more likely to get sick again in the future. At the moment, there are no medicines to help prevent or treat delirium. The people doing this research want to find out if a drug called dexamethasone can help stop people from getting delirium after surgery for their broken hip. Before we do a very large study to investigate this question, we will do a smaller study first to decide how best to answer this research question.

Aims

The aim of this research is to confirm how best to run a large research study to see whether dexamethasone makes things better for people who might get delirium after their surgery.

Research plan

94 patients with a broken hip will be asked to take part. After agreeing to take part, they will then be placed in one of two groups: one getting usual care, and the other getting usual care plus an injection of dexamethasone before their surgery. We will check to see how many patients get delirium in the first five days after surgery. We will also ask patients how well they feel, where they live and how well they can move around. This will help us decide whether we should do a larger study with more patients to confirm whether patients with broken hips benefit from dexamethasone.

Getting the results out

The results will be shared with doctors and nurses as well as patients and public. They will work together to make sure that patients get the best care possible. We will publish our findings in scientific journals and reports to help get the messages out. We hope that organisations that set national standards for how we provide care for people with a broken hip will use the findings from this research as well.

4 DELPHIC SYNOPSIS

Comparison title	World Hip Trauma Evaluation – DELPHIC: A pilot randomised trial of Delirium prevention in Fragility Hip Fractures with Corticosteroids			
Short title	WHiTE-16 DELPHIC			
Registration	The comparison has been registered with the current controlled trials database ISRCTN <TBC>; and with the Research Delivery Network NIHR CPMS ID 59647			
Funder for DELPHIC	Department of Health – NIHR Research for Patient Benefit Programme *Support from the NIHR Oxford Biomedical Research Centre*			
Design	A multi-centre, parallel-group, randomised, controlled external pilot trial.			
Participants	All patients 60 years and over with a hip fracture who in the opinion of the treating surgeon may benefit from surgical treatment and meet DELPHIC specific eligibility criteria are eligible to take part in this comparison. Patients who lack capacity may be entered into the comparison under consent from a legal representative.			
Sample Size	94			
Comparison Duration	28 months. Total length of project: 28 months - 8 months set-up, 13 months recruitment, 2 months follow-up, 5 months data cleaning, analysis and report writing. Participants will be followed up to 4 months post-diagnosis of a hip fracture.			
	DELPHIC Objectives	**Instruments**	**Timepoint(s)**	
			Part of Platform common outcome set	**DELPHIC-specific**
Primary	1) To confirm willingness of patients and healthcare professionals to participate in this randomised comparison.	Recruitment rate	N/A	**Recruitment and screening log:** Baseline
Secondary	2) To confirm whether there is an indication of a meaningful effect in the primary outcome (peak MDAS score) of the proposed definitive randomised comparison	Memorial Delirium Assessment Scale (MDAS)	N/A	**Participant:** Days 1-5 post-surgery
	3) To confirm process practicality in terms of intervention delivery and data collection for a definitive randomised comparison.	MDAS, FPS/ PAINAD, TICS, EQ-5D-5L, Emotional Distress, mNMS and	**Participant:** Baseline and 4 months post-diagnosis of a hip fracture (EQ-5D-5L, mNMS,	**Participant:** Pre-surgery (FPS/PAINAD), Days 1-5 post-surgery (MDAS, FPS/PAINAD &)

		CRFs for Residential Status, Death Notification, Complications, Resource use	Residential status, resource use) 4 months post-diagnosis only: Death Notification, Complications **Medical record check:** Discharge	4 months post-diagnosis of a hip fracture (Emotional Distress & TICS) **Medical record check:** If indicated at 4 months post-diagnosis of a hip fracture
Intervention - IMP	Intravenous bolus of 13.2 mg dexamethasone base (equivalent to 16 mg dexamethasone phosphate) at the start of anaesthesia			
Control – Standard care	As per routine practice at each recruitment centre.			

5 ABBREVIATIONS

AR	As Randomised
CRF	Case Report Form
CTIMP	Clinical Trial of an Investigational Medicinal Product
DSUR	Development Safety Update Report
DSMC	Data and Safety Monitoring Committee
EQ-5D-5L	EuroQol 5 Dimension 5 Level
FPS	Functional Pain Scale
GP	General practitioner
HRQoL	Health Related Quality of Life
IMP	Investigational Medicinal Product
ITT	Intention to Treat
LLI	Local Lead Investigator
MDAS	Memorial Delirium Assessment Scale
MHRA	Medicines and Healthcare products Regulatory Agency
mNMS	Modified New Mobility Score
NDORMS	Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences
NHFD	National Hip Fracture Database
NHS	National Health Service
NIHR	National Institute for Health and Care Research
OCTRU	Oxford Clinical Trials Research Unit
PAINAD	Pain Assessment in Advanced Dementia
PI	Principal Investigator
POC	Platform Oversight Committee
PP	Per Protocol
RSI	Reference Safety Information
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedure
SAR	Serious Adverse Reaction
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TICS	Telephone Interview for Cognitive Status

WHiTE	World Hip Trauma Evaluation

6 BACKGROUND AND RATIONALE

6.1 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.[1,13,24] 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 fractures suffered with post-operative delirium.[27,33] 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.[18,19] 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.[25]

In this comparison we will investigate if an injection of corticosteroids just before the 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 4 months.[14]

6.2 How does the existing literature support this proposal?

Postoperative delirium in older people can be attributed to modifiable (inflammation, disturbance of sleep-wake cycle) and non-modifiable (intrinsic brain vulnerability, dementia) factors. Inflammation due to surgery and trauma is communicated to the brain through the vagus nerve, transferred across the blood-brain-barrier through transport proteins and directly to the brain in areas that lack a blood-brain-barrier.[21]

The association between levels of inflammation before surgery (assessed by measuring cytokines in the blood) and the development of postoperative delirium is widely accepted and is supported by the findings of our recent systematic review.[28] Elevated serum interleukin-6 (a marker of inflammation) before surgery, is associated with an increased risk of postoperative delirium, making reduction of inflammation a potential therapeutic target to reduce the risk of post-operative delirium.

People with hip fracture are at particular risk of delirium due to the combination of pre-existing vulnerabilities (age, poor cognitive reserve) and the inflammatory impact of the hip fracture and surgery to repair it. There is increasing interest in re-purposing anti-inflammatory drugs, which can reduce the inflammatory response around the time of surgery, to reduce the risk and severity of delirium.

Corticosteroid drugs, including dexamethasone, are anti-inflammatory drugs commonly used for many conditions. Dexamethasone is widely available in the NHS with multiple uses including reduction of swelling around brain tumours[22] and reduction of mortality in people with severe COVID-19.[16] It has been used widely for many years in the UK and around the world in the perioperative period as a prophylactic antiemetic in patients undergoing surgery.[8,35]

We systematically searched trial registries and publication databases updating previous systematic reviews for ongoing and published trials concerning corticosteroids, surgery and delirium. There is pilot evidence suggesting benefits of corticosteroids on postoperative delirium prevention in hip fracture

patients. We identified ten published randomised controlled trials on the effect of administration of corticosteroids on postoperative delirium: cardiac surgery [n=5],[11,26,34,37] hip fracture [n=3], [6,20,38] and gastrointestinal surgery [n=2]. [3,38]

The hip fracture trials included people aged ≥ 65 years. The corticosteroids were dexamethasone (20 mg, n = 79) [20] (10 mg, n = 160)[39] and methylprednisolone (125 mg, approximately equivalent to 25 mg dexamethasone, n = 122).[6] They demonstrated a reduction in the incidence[6,39] and severity of delirium.[20,39] These trials demonstrate feasibility of administration of corticosteroids in the peri-operative period for the purpose of delirium prevention or amelioration. However, both were single centre, conducted outside the NHS setting, relatively small and do not provide definitive practice-changing evidence. There is one ongoing trial (n = 230) listed on the Chinese Trials Registry (ChiCTR2200066552) with relatively restrictive inclusion criteria – notably excluding those who are more comorbid and those with dementia. With minor exceptions, the anti-inflammatory dose of dexamethasone is 6.6-13.2mg. The higher end of this dose range was chosen for the comparison to reflect the increased glucocorticoid requirements at the time of surgery.[40,41] This is a dose within the range used by the studies detailed above [6,20,39]. Of note, the dose of dexamethasone is variously given as total mass of drug or a dexamethasone base. DELPHIC is using the current preferred approach of dexamethasone base. The DELPHIC dose of 13.2mg is equivalent to 16mg of total dexamethasone.

In summary, there is biological plausibility, and limited trial evidence, that corticosteroids will reduce delirium severity and incidence with a strong track record of safety in perioperative use.

6.3 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. The aim of this pilot comparison is to inform the planning assumptions needed for a definitive, pragmatic multi-centre randomised controlled trial of intravenous dexamethasone immediately prior to surgery compared with standard care on the severity of postoperative delirium.

7 OBJECTIVES AND OUTCOME MEASURES

7.1 Primary objective

1. To confirm willingness of patients and healthcare professionals to participate in this randomised comparison.

7.2 Secondary objectives

2. To confirm whether there is an indication of a meaningful effect in the primary outcome (peak MDAS score) of the proposed definitive randomised comparison.
3. To confirm process practicality in terms of intervention delivery and data collection for a definitive randomised comparison (data collection will be that of the Platform common outcome set)

7.3 Outcome measures

In order to determine the process practicality of data collection for a full randomised control trial, 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-months post-diagnosis of a hip fracture t. These are EQ-5D-5L, mNMS, UKNHFD Residential Status, Resource Use, Death Notification, Complications, Medical records check. Additional (clinical) outcomes specific for this randomised comparison are:

Delirium

Peak post-operative delirium will be measured by the Memorial Delirium Assessment Scale (MDAS)**.** Participants will be assessed once daily after the surgical repair of the hip fracture using the MDAS[5] 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[24]. 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. 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 data from this outcome will be used to address objective 2 of this pilot comparison, which will become the primary objective of the full scale study should this comparison be deemed feasible.

Pain

Pain will be assessed using the Functional Pain Scale (FPS) for use in hospitals,[2,12] which is a validated 5-point scale that assesses the activities that pain limits rather than rating severity of pain. For participants unable to communicate due to mental capacity (estimated to be approximately 10% of the comparison sample) the validated Pain Assessment in People with Advanced Dementia (PAINAD)[23,36] tool will be used. PAINAD is a five-domain score ranging from 0-10. FPS / PAINAD will be collected pre-surgery and on each of the first 5 days post-surgery by a delegated member of the research team.

Cognitive impairment

Participants will provide responses in order to complete the TICS UK English 2014 questionnaire to assess Cognitive Impairment at 4 months post-diagnosis of a hip fracture.[4,10] Since most people treated for a hip fracture in the UK are not followed up in person after being discharged from hospital, the 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.

Emotional distress

Emotional distress will be measured using the Distress Thermometer, a widely used 0–10 scale to assess current or recent levels of distress. [31] Survivors of delirium frequently cite the emotional distress of delirium among the most unpleasant aspects of the condition [29] and it has been shown to remain elevated up to a year after surgery. [30] Distress will be measured at the 4 month follow up time-point and asked of participants who achieved an MDAS score of 13 or higher following the surgery, as this score indicates the presence of delirium. It is also one of six outcomes in the recently published Core Outcome Set for Delirium prevention trials. [32]

Complications

The expected complications for the comparison are detailed in section 11.1 of this protocol appendix. 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. To facilitate collection of complications as per section 12.3.5 of the Platform Master Protocol, medical records for all participants will be reviewed by appropriately trained staff at discharge and if indicated, at 4 months post diagnosis of hip fracture.

Specific attention will be paid to surgical site infection. Diagnosis of deep infection will be according to the Centre of Disease Control definition.[15] This definition stipulates that the diagnosis can be made up to 90 days post-surgery. Upon indication of potential deep surgical site infection in the participant report at 4 months, the recruitment centre 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.

Recruitment rate

In addition, the clinical outcomes listed above which will be used to address objectives 1 and 3 of this comparison, we will also collect data on recruitment (dates relating to site set-up, recruitment period and numbers approached, consented and randomised) to address objective 2. The main measure will be recruitment rate (recruited divided by number of days sites are open to recruitment).

8 DESIGN

8.1 Concept

This is a multi-centre, parallel-group, randomised, controlled external pilot comparison embedded within the overarching WHiTE Platform.

The main aim is to inform the planning assumptions needed for a definitive, pragmatic multi-centre randomised controlled trial of intravenous dexamethasone immediately prior to surgery compared with standard care on the severity of postoperative delirium. Participants will be recruited from 8 recruiting centres across the UK.

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

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 (or legal representatives) who decline consent or withdraw will be recorded.

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.

An assessment of post-operative delirium will be made using the peak MDAS which will be recorded each day during the first five days after surgery. Levels of emotional distress will also be measured at 4 month follow up time point using the Distress Thermometer.

At 4-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[8] to collect self-reported or proxy-reported information.

9 COMPARISON PROCEDURES

A comparison flow chart is provided in Annex A.

9.1 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. Acute uncontrolled infection as diagnosed by the treating clinician.

2. Hypersensitivity to dexamethasone or excipients within the preparation
3. Use of oral or / intravenous corticosteroids at or following admission.
4. Concurrent participation in a conflicting clinical trial of an investigational medicinal product
5. Receipt of a live vaccine within 2 weeks prior to treatment
6. Known gastrointestinal ulcer
7. Congestive cardiac failure
8. History of steroid psychosis
9. Current glaucoma or corneal ulcer
10. Severe ulcerative colitis
11. Active diverticulitis
12. Suspected or confirmed strongyloidiasis
13. Known history of tuberculosis

Exclusion criteria, in particular relating to contraindications, have been prepared in line with the Summary of Product Characteristics (SmPC) as is relevant to a one-off dose of systemic administration of dexamethasone. Eligibility for entry into the comparison will be confirmed by a medically qualified person.

9.2 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 Section 11.4 of the Platform Master Protocol will apply.

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

9.3 Randomisation

Randomisation will be as per section 11.5 of the Platform Master Protocol. Randomisation will be on a 1:1 basis to standard of care plus dexamethasone or standard of care, stratified by recruitment centre and the presence/absence of cognitive impairment at presentation (proxy consent will be used as a surrogate indicator for lack of cognitive impairment). 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.

9.4 Blinding and code-breaking

The participant and the local research team members involved in the delirium assessment and data collection process will be blinded to the allocated treatment. When applicable following randomisation, an appropriately qualified anaesthetist will prepare and administer the comparison intervention and therefore will not be blinded. In order to maintain blinding amongst the relevant members of staff, robust training will be provided to recruitment centres to ensure details of treatment administration are entered onto the study data collection system only after all primary outcome assessments have been completed.

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 Principal Investigator (PI) or Local Lead Investigator (LLI) will be forwarded to an authorised member of the central trial team. If the person requiring the unblinding is not the PI or LLI 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 steps available on the randomisation system procedure available for unblinding.

On receipt of the treatment allocation details the PI, LLI or treating health care professional will continue to deal with the participant's medical emergency as appropriate. The individual 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 participant's subfolder accessible only to authorised members of the central trial team.

9.5 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 table 1 below:

Time Point	Data	Source	Setting
Enrolment	i) Eligibility screen ii) Informed consent	Screening form and consent form	Acute inpatient - face to face;
Pre-surgery*	i) FPS/PAINAD	Participant or proxy	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
Days 1-5 post-surgery*	i) MDAS ii) FPS/PAINAD iii) Opioid use	Participant Medical records	Acute inpatient - face to face; Medical record review
Up to point of discharge	i) Early complications ii) Treatment administration	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 vii) Emotional Distress*	Participant or proxy & medical record	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*

9.5.2 Visits and Contacts

Contact 1: Pre-operatively, FPS/PAINAD will be collected on the hospital ward to determine baseline pain level.

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

Contacts 3-7: Days 1-5 after the day of surgery, delirium assessments will be made on the hospital ward by trained staff using the MDAS. A pain score and opioid use will also be collected.

Contact 8: Follow-up at 4 months post-diagnosis of a hip fracture as per Platform Master Protocol with the addition of TICS and Emotional Distress (emotional distress only collected for those scoring 13 or higher in MDAS, as per section 7.5).

9.6 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 4 months post-diagnosis of a hip fracture of the last participant. The Sponsor, MHRA and REC will be notified in writing if the comparison has been concluded or terminated early.

10 INTERVENTIONS

10.1 Description of the randomised treatments

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

- Intervention: A single intravenous injection of 13.2 mg of dexamethasone.
- Control: Standard care

The IMP, dexamethasone, has marketing authorisation and is routinely used in perioperative clinical practice as an anti-emetic at slightly lower doses (3.3 – 6.6 mg). It is being used outside of its licensed indication (postoperative nausea and vomiting) but safety profile in the comparison population is expected to be the same. Similar doses to DELPHIC are routinely used in elective orthopaedic arthroplasty practice; higher doses are routinely used for days or weeks before and after neurosurgery; and recent trials have demonstrated safety of much higher doses (1mg/kg) in the higher risk emergency laparotomy population.[42] It will be prepared as per section 10.1.1 below prior to administration. Dexamethasone is described only by its active ingredient and any brand can be used for this randomised comparison.

10.1.1 Labelling, Storage and Administration of the IMP

The IMP will be used from standard stock held in the operating theatre and will not be labelled with a Clinical Trial Label; nor will the packaging be blinded as there is no placebo being used in this comparison.

An appropriately trained clinician not involved in the assessment of any comparison outcomes will carry out the online treatment allocation reveal process. The name of the person administering the intervention treatment will be recorded on the treatment CRF.

The treating anaesthetist will prepare a syringe with the allocated intervention, in an area away from the rest of the clinical team and any blinded members of the research team so as not to reveal the treatment allocation to potential blinded assessors. The prepared syringe will then be labelled dexamethasone 13.2 mg in accordance with local practice.

Participants randomised to the intervention group will be given a single intravenous administration of 13.2mg dexamethasone. This solution will be drawn up directly from vials containing 3.3 mg/ml Solution of dexamethasone.[1] No dilution is required. The attending anaesthetist will give the intervention as an intravenous bolus (as is standard practice) at the time of induction of anaesthesia or administration of spinal anaesthesia. It will be drawn up just prior to administration. The preparation and administration of the IMP will be done when blinded staff are not in the operating theater to avoid any accidental unblinding.

Participants randomised to the control group will receive the standard of care as is routine at each recruitment centre, there will be nothing additional as part of this protocol.

10.1.2 Accountability of the Comparison Treatment

As this is a pragmatic randomised comparison involving a one-off administration of the intervention in a context where it is frequently administered at similar or higher doses, by clinically trained professionals, a

[1] A note on formulation / dose. Dexamethasone is currently defined by mass of dexamethasone base, whereas previously it was typically defined by mass of the dexamethasone salt (dexamethasone phosphate). Older literature typically refers to multiples of 4mg of dexamethasone phosphate. Correct prescribing is now for the base alone, which is therefore in multiples of 3.2mg (the contents of one vial)

risk adapted approach has been employed to ensure the appropriate level of documentation is kept to record IMP accountability as per standard local practice. The total dose of administered treatment will be collected.

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

High doses of corticosteroids are intended for short term therapy and therefore adverse reactions are uncommon. Peptic ulceration and bronchospasm are rare reactions that may occur. Except for hypersensitivity, other significant adverse effects have only been associated with prolonged systemic corticosteroid therapy. Due to the one-off dose being administered in this comparison, these symptoms are not expected for this participant population. Rarely a mild increase in blood sugar levels may occur which returns to normal within 24 hours, this can be more common in people with diabetes but there is no evidence that this is clinically significant.

10.1.5 Efficacy of the IMP

Three previous trials in hip fracture have suggested efficacy of dexamethasone to reduce the incidence or severity of postoperative delirium following hip fracture surgery (see section 6.2).

10.1.6 Concomitant Medications

Section 4.5 of the SmPC should be referred to for concomitant medications to avoid prior to and during dosing with Dexamethasone. Additionally, in accordance with section 4.4 of the SmPC live vaccines are not to be administered within 8 weeks after treatment.

10.1.7 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.

11 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 4 months post-diagnosis of a hip fracture. This section details the SAE reporting requirements specifically for the IMP in this comparison **and are in addition to those detailed within section 15 of the Platform Master Protocol.**

As the safety profile of dexamethasone is very well known, only related SAEs will be reported for this comparison. Investigators should follow up serious adverse events until resolved or until stabilisation or resolution.

11.1 Recording and reporting of adverse events/serious adverse events related to the IMP

High doses of dexamethasone are intended for short term therapy and therefore adverse reactions are uncommon. As the safety profile of dexamethasone is very well known, only SAEs considered related to the IMP by the Principal Investigator (or delegate) will be reportable as an SAE for this comparison, unless the SAE is exempt from reporting (see below).

11.2 SAEs exempt from reporting for this comparison

In line with expected events within this dose, in accordance with the RSI used within the dexamethasone SmPC, The following expected SAE is exempt from reporting as a SAE for this comparison only and will be collected on the complications CRF for this comparison:

- Disturbances of blood glucose homeostasis requiring either:

1. a new intravenous insulin infusion, or
2. administration/increasing dose of an oral hypoglycaemic agent

11.3 Reporting Procedure

Unless excluded from reporting as a SAE, SAEs should be reported in accordance with section 15.3.4 of the Platform Master Protocol.

11.4 Expectedness

See Platform Master Protocol section 15.4 for 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.

12 STATISTICS & ANALYSES

12.1 Sample Size Determination

The proposed sample size for the external pilot phase is 94 participants.[7] A pilot sample size of 94 is required to produce an upper limit of a one-sided 90%confidence interval which excludes 2.5 mean difference in the peak MDAS (a clinically important one), given a SD of 8.4, assuming that the treatment estimate from the pilot was zero or less, and cautiously accounting for 20% loss of primary outcome.

12.2 Analysis Populations

The primary analysis population of interest will be focused upon “intention to treat” principle; that is all participants will be analysed “as randomised” (AR). Sensitivity analyses will be undertaken on the per-protocol (PP) analysis set (see below) for the primary outcome. Secondary outcome will be summarised based upon the AR analysis set.

The AR analysis set will include all randomised participants including:

1. Participants who are randomised, undergo surgery and receive their randomly allocated intervention

2. Participants who are randomised but do not undergo surgery for whatever reason.

3. Participants who are randomised and found to be ineligible before, during or after surgery.

4. Participants who receive surgery but do not get their randomly allocated intervention.

Note: participants who withdraw from the comparison between randomisation and 4 months post-diagnosis of a hip fracture will provide data up to the point of withdrawal.

The 'PP' analysis set will be the AR analysis set excluding participants as described in 2-4 above and other major deviations from the protocol which will be fully described in the Statistical Analysis Plan.

12.3 The Level of Statistical Significance

A one-sided p-value will be reported for MDAS only along with one-sided 90% confidence interval. Other clinical outcomes will only be descriptively summarised without any formal comparison or calculation of associated uncertainty. Feasibility measure (e.g. completion of primary outcome) will be reported at the 2-sided 95% confidence level where appropriate.

12.4 Analysis

Principal analysis of the primary outcome will estimate the average treatment effect ("as randomised groups"), without imputation of missing outcome data. A linear regression model will be used to compare peak MDAS between groups, adjusting for the randomisation variables, will be used to estimate uncertainty in peak MDAS as the aforementioned one-sided 90% CI to indicate the maximum plausible treatment effect (in favour of dexamethasone use). Sensitivity analyses of the primary outcome will explore the influence of compliance (PP analysis using the PP analysis set) and missing data where substantial (10% or more) and/or in presence of differential missing data. Secondary outcomes will be summarized by trial group with the uncertainty in treatment effect using generalised linear models and reported with uncertainty (at an equivalent statistical significance level using 2-sided 80% confidence interval).

Baseline demographic data will be summarised by treatment groups. 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. Completion of outcomes will be quantified and report with uncertainty (95% confidence interval using Wilson method's, e.g. using the ci command in Stata).

No separate statistical analysis plan (SAP) will be drafted given the formal analyses as fully reported as above.

13 DISSEMINATION POLICY

Outputs with regards the primary objective of this comparison will be submitted for publication within 12 months 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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15 ANNEX A: FLOW CHART

Inclusion Criterion:

Adults aged 60 years or over diagnosed with a hip fracture that in the opinion of the treating surgeon may benefit from surgical treatment.

Exclusion Criteria:

1. Acute uncontrolled infection as diagnosed by the treating clinician.
2. Hypersensitivity to dexamethasone or excipients within the preparation
3. Use of oral or / intravenous corticosteroids at or following admission.
4. Concurrent participation in a conflicting clinical trial of an investigational medicinal product.
5. Receipt of a live vaccine within 2 weeks prior to treatment
6. Known gastrointestinal ulcer
7. Congestive cardiac failure
8. History of steroid psychosis
9. Current glaucoma or corneal ulcer
10. Severe ulcerative colitis
11. Active diverticulitis
12. Suspected or confirmed strongyloidiasis
13. Known history of tuberculosis

Additional Exclusion criteria (Platform):

14. Previous participation in the same randomised comparison.

15. A second hip fracture (other side) while the patient is still enrolled in the platform following their first hip fracture.