Master Protocol:

World Hip Trauma Evaluation (WHiTE) Platform – a framework for clinical trials for fragility hip fracture in those aged 60 and over

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Master Protocol: World Hip Trauma Evaluation (WHiTE) Platform – a framework for clinical trials for fragility hip fracture in those aged 60 and over

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This document describes the overall plan and structure for the WHiTE Trials Platform. A separate document (appendix to this master) will be created for each of the randomised comparisons.

We declare no conflicts of interest.

This project is conducted in compliance with the Declaration of Helsinki (2013), the Principles of Good Clinical Practice, the General Data Protection Regulation & UK Data Protection Act (2018), the UK Statutory Instrument 2004/1031 for drug trials and subsequent amendments, the UK Statutory Instrument 2002/618, Medical Devices Regulations and the UK Health Service Research Governance Framework for Health and Social Care.

This project is being coordinated under the standard operating procedures of the UKCRC registered Oxford Clinical Trials Research Unit (OCTRU) at the University of Oxford.

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.

Platform Chief Investigator Signature:

Statistician Signature:

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1 AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
N/A – part of initial submission	2.0	08Jan2021	Amrita Athwal	Insertion of reference numbers and contact email addresses. Update to GDPR Information (Section 18.2)
AM02 (SA 01)	3.0	28Apr2021	Stephanie Wallis, Amrita Athwal	Addition of DSMC member to p.9 Correction of terminology; replacing of the word 'study' throughout the document to more accurately reflect the platform of work 11.4.5 Removal of incorrect sentence relating to non-CTIMP consenting procedures in Scotland 11.4.8 Correction of procedures relating to consent following loss of capacity of participant
AM06 (SA 02)	4.0	14Oct2021	Amrita Athwal	Re-naming of sponsor representative office to Research Governance, Ethics & Assurance (RGEA) 10.3 Addition of exclusion criteria text to clarify eligibility of contralateral fractures as well as patients not being enrolled more than once into a comparison 18.1 & 18.2 Text and data flow diagram updated to include data linkage to National Joint Registry (NJR)
AM11 (SA 04)	5.0	08Jun2022	Amrita Athwal Juul Achten	Addition of a new randomised comparison within the Platform framework: Appendix 12 – DUALITY. Non-CTIMP study looking at dual mobility versus standard articulation total hip replacement in the treatment of older adults with a hip fracture. Standardisation of index time-point (post-diagnosis of a hip fracture) and references to recruitment centre throughout the protocol. 12.3.5 Clarification of cross-checking of participant-reported complications 18 Correction of heading 18.2 Correction of arrowheads in data flow diagram (figure 2)

				18.3 edits to analysis methods wording to ensure these remain applicable to all future comparisons 19.1 Clarification that source data definitions will be further defined in each appendix.
AM14 (SA 05)	6.0	16Dec2022	Amrita Athwal, Xavier Griffin	Page 2 Sponsor contact details updated. Section 4, 7 and 12.3.3 The UK National Hip Fracture Database Mobility Scale is the current outcome measure to compare mobility. This has been replaced with a new validated tool called the modified New Mobility Score as it was noted that this would provide better quality data to inform the mobility objective. To reflect this an updated statistics sections has been included to FRUITI and LIT protocol appendices to allow for management of data collected using the previous mobility scale. 4 Synopsis table and 7.2 outcomes table wording of outcomes updated: rewording/clarification of short-term and long-term objectives to align more accurately with plans for analysis. 5 Updates to abbreviations list9.1 Clarification of PI arrangements at recruiting centres for the overall WHiTE Platform and investigator arrangements for individual randomised comparisons 11.4.7 Minor clarification of procedures should a participant regain capacity 11.4.9 Addition of process of documenting witness signature during consent process when a participant is physically unable to sign a consent form 12.4 introduction of electronic welcome and anticipatory follow-up time-point messages to participants (email/SMS). 20.2 Updates to central study team monitoring arrangements. Typographical errors corrections.
AM17(SA 06)	6.0	23May2023	Kate Herbert, Juul Achten	Addition of a new randomised comparison within the Platform

				framework: Appendix 14 – PRESSURE 3. Non-CTIMP study assessing early heel specific adjunct devices for heel pressure ulcer prevention in people with a fractured hip.
AM19 (SA 07)	7.0	TBD	Elisa Basso, Juul Achten	Addition of a new randomised comparison within the Platform framework: Appendix 13 -Delirium and Cognitive Impairment (DECI). CTIMP study investigating if infusion of anti-TNF during surgery has an effect on delirium symptoms in the immediate post-operative period. Updates/clarifications to master protocol: Update address Deputy CI, Update sponsor email address, Update to the Funder name, Update to chair of DSMC. Update to table 1 'Amendment history' to include full description of new randomised comparisons to the WHiTE Platform – please see section for AM11 (SA 04) and section for AM17 (SA 06). Section 4 Clarification mortality risk will be assessed up to 4 months post-diagnosis. Section 9.1 Clarification Principal Investigator at recruitment centre needs to be medically qualified person. Clarification that local lead investigator for the oversight of a particular randomised comparison can be a health care professional with a certain specialty if deemed more suitable for that comparison. Section 11.6 Created heading for blinding information and made reference to further information in appendix protocol. Section 14 clarification data routine collection for participants who withdrew from a randomised comparison(s). Section 17.1 clarification full economic evaluation will only be conducted when funding is available. Section 19.8 update data retention to 5 years for both CTIMP and non-CTIMP randomised comparisons.

				Section 23.4 location of log of amendments updated. Section 25.1 Removal of INVOLVE conference, more generic wording included.

2 KEY CONTACTS

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3 SUMMARY

Hip fracture is one of the biggest challenges facing patients and healthcare systems. Worldwide there are 1.3 million hip fractures with more than 70,000 hip fractures in the UK every year.[1,2] These figures are projected to rise to more than 6 million by 2050 worldwide.[3] The global cost of this clinical problem is estimated at 1.75 million disability adjusted life years lost and represents 1.4% of the total healthcare burden in established market economies.[1,4] People suffering hip fracture have a 30-day mortality rate of 7%, a 1-year mortality rate of 25% and experience a permanent reduction in their health-related quality-of-life similar to that of a patient with Parkinson's disease or multiple sclerosis.[5]

WHiTE is a platform trials framework, designed to efficiently deliver multiple randomised comparisons of interventions for patients aged 60 years and over with a hip fracture. It is based upon experience derived from the planning and delivery of a related group of randomised trials of interventions for hip fracture. The purpose of the platform is to simplify the patient pathway through research in this field and capture efficiencies in the reduction of documents and clinical reporting forms duplication. Furthermore, the proposed platform is more coherent with a single set of ethical and regulatory approvals and an explicit legal basis and processing purpose for the use of patient-level data.

This Master Protocol facilitates and streamlines the efficiency of trials with a common core dataset and documentation. It describes those components of the research process which will be consistent between randomised comparisons. Where additional procedures are planned, specific to a randomised comparison – for example the collection of additional outcome data - these will be described in a separate appendix for that randomised comparison. The individual appendices are not dependent on each other and each will have its unique start and stop dates and publication of results without compromising the integrity of the platform. It should be noted that, in the event that a CTIMP appendix ends and there are no current CTIMP appendices, the platform will remain open for the future addition of other CTIMPs. It is anticipated that randomised comparisons including medical devices will be added which will be subject to substantial amendments and the addition of relevant instructions.

All patients aged 60 years and over with a hip fracture presenting to the WHiTE recruitment centres will be considered for eligibility for each of the randomised comparisons. They will be offered the opportunity to take part in any or all of the randomised comparisons for which they are eligible. Comparisons may be contemporaneous or distributed throughout the treatment pathway. As new randomised comparisons are added to the WHiTE platform, they will be assigned a unique numeric identifier (i.e. WHiTE 11, WHiTE 12, etc) and a separate appendix to this Master Protocol will be created.

Eligibility for each randomised comparison will be assessed against the specific criteria described in the relevant appendix. Interventions may be simple, complex or multimodal. E.g. investigational medicinal products, surgical interventions or care pathways; delivered at any stage along the diagnostic, treatment and rehabilitation pathway. Figure 1 provides an illustration of flow through the platform with four hypothetical randomised comparisons (A-D).

This project was developed by a team of patient representatives, clinical experts in trauma orthopaedics, trial management specialists, experienced statisticians and health economists. The Oxford Clinical Trials Research Unit, based at the University of Oxford, will provide the quality management framework for the programme to help assure the quality of the Platform and the appended randomised comparisons, and

will audit as appropriate. A Platform Oversight Committee (POC) of patient representatives and independent experts will oversee its progress and conduct.

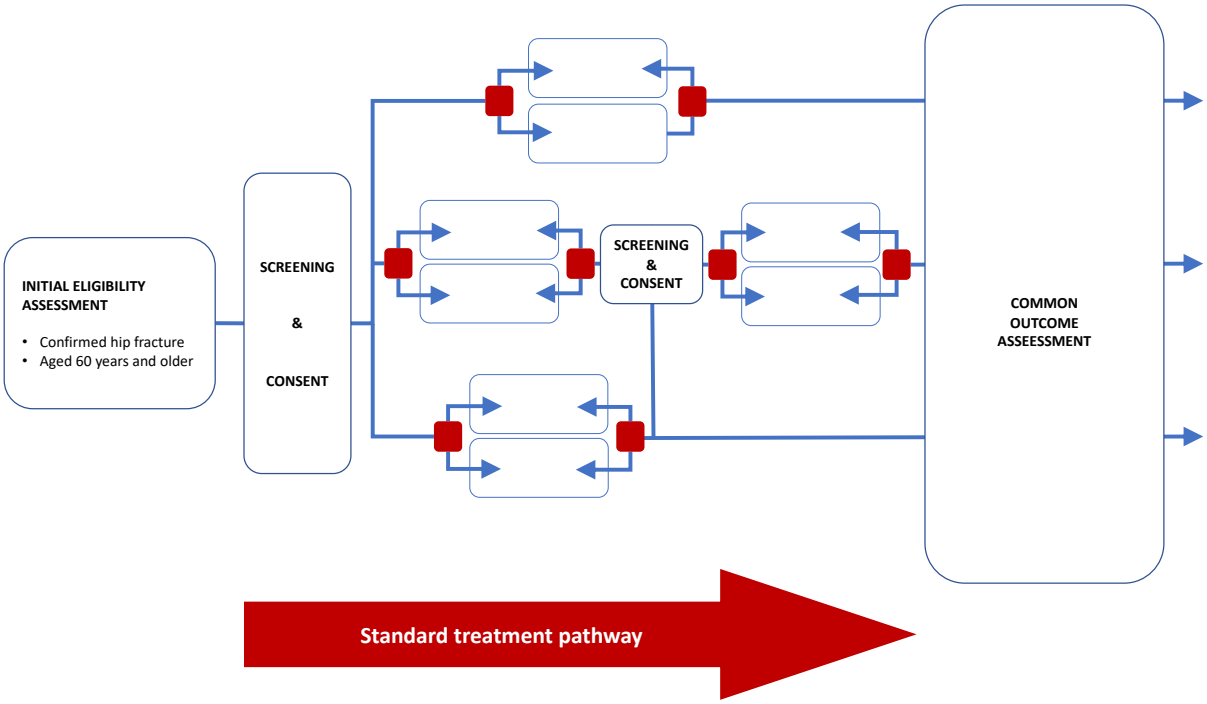

Figure 1: WHiTE Platform summary. Key: 1/2 are randomly assigned treatment alternatives for clinical treatments A, B, C & D

4 SYNOPSIS

Title	World Hip Trauma Evaluation (WHiTE) Platform – a framework for clinical trials for fragility hip fracture		
Short title	WHiTE Platform		
Registration	The Platform has been registered with EudraCT Ref: 2020-003719-83		
Sponsor	University of Oxford		
Funder	Department of Health – NIHR Oxford Biomedical Research Centre		
Design	Platform for the delivery of multicentre randomised clinical trials for patients with hip fracture		
Participants	All patients 60 years of age and over presenting to a WHiTE recruitment centre for treatment of a hip fracture		
Duration	Perpetual; no fixed project length for the platform. The duration of involvement will be dependent upon the number and specifics of the comparison intervention(s) participants take part in, which may last the individuals' lifetime. Each randomised comparison will have specified start and end points which will be described in the relevant appendix.		
Common Outcome Set	**Objectives**	**Outcome Measures**	**Timepoint(s)**
Short-term outcomes	To compare health-related quality-of-life (HRQoL) between treatment groups	EuroQol 5 Dimensions 5 levels (EQ-5D-5L)	Baseline and at 4 months post-diagnosis of a hip fracture
	To compare mobility between treatment groups	modified New Mobility Score (mNMS)	Baseline and at 4 months post-diagnosis of a hip fracture
	To compare residential status between treatment groups	UK National Hip Fracture Database Residential Status	Baseline and at 4 months post-diagnosis of a hip fracture
	To compare mortality risk between treatment groups	Death notification	Up to 4 months post-diagnosis of a hip fracture
	To compare risk and pattern of complications between treatment groups	Complications CRF, medical records check	Baseline and at 4 months post-diagnosis of a hip fracture
	To compare the healthcare and broader resource implications between treatment groups	Review of hospital medical notes complemented by patient-completed resource use questionnaire	Baseline and at 4 months post-diagnosis of a hip fracture
Long-term outcomes	To compare risk and pattern of complications between treatment groups	Bespoke diagnostic and procedural events within linked routinely collected databases	Up to final appendix-specific follow-up time-point
	To compare the healthcare and broader resource implications between treatment groups	Bespoke diagnostic and procedural events & healthcare contact reimbursement data within linked routinely collected databases	Up to final appendix-specific follow-up time-point
	To compare mortality risk between treatment groups	Linked routinely collected registers of death events and attributed causes	Up to final appendix-specific follow-up time-point

5 ABBREVIATIONS

AE	Adverse Event
AR	Adverse reaction
BOA	British Orthopaedic Association
CI	Chief Investigator
CMG	Comparison Management Group
CRF	Case Report Form
CT	Clinical Trials
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of an Investigational Medicinal Product
DSMC	Data and Safety Monitoring Committee
DSUR	Development Safety Update Report
eCRF	Electronic Case Report Form
EFORT	European Federation of National Associations of Orthopaedics and Traumatology
eISF	Electronic Investigator Site File
EQ-5D-5L	EuroQol 5 Dimension 5 Level
EudraCT	European Union Drug Regulating Authorities Clinical Trials (database)
GCP	Good Clinical Practice
FFN	Fragility Fracture Network
GDPR	General Data Protection Regulation
GP	General Practitioner
HEAP	Health Economics Analysis Plan
HES	Hospital Episode Statistics
HRA	Health Research Authority
HRQoL	Health Related Quality of Life
IB	Investigator's Brochure
ICD	International Statistical Classification of Diseases and Related Health Problems
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
IP	Intellectual Property
ITT	Intention to Treat
INMB	Incremental Net Monetary Benefit
MCAR	Missing completely at random

MHRA	Medicines and Healthcare products Regulatory Agency
NDORMS	Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences
NHFD	National Hip Fracture Database
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
NIHR BRC	NIHR Biomedical Research Centre
NJR	National Joint Registry
mNMS	modified New Mobility Score
OCTRU	Oxford Clinical Trials Research Unit
OPCS	Office of Population Censuses and Surveys
OTA	Orthopaedic Trauma Association
OTS	Orthopaedic Trauma Society
PEDW	Patient Episode Database for Wales
PI	Principal Investigator
PIS	Participant/ Patient Information Sheet
PMG	Platform Management Group
POC	Platform Oversight Committee
QALY	Quality Adjusted Life Year
R&D	NHS Trust R&D Department
REC	Research Ethics Committee
RGEA	Research Governance, Ethics & Assurance
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SHFA	Scottish Hip Fracture Audit
SmPC	Summary of Product Characteristics
SMS	Short Messaging Service
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
WHiTE	World Hip Trauma Evaluation

6 BACKGROUND AND RATIONALE

6.1 What is the clinical problem being addressed?

Hip fracture is one of the biggest challenges facing patients and healthcare systems. Worldwide there are 1.3 million hip fractures with more than 70,000 hip fractures in the UK every year.[1,2] These figures are projected to rise to more than 6 million by 2050 worldwide.[3] The global cost of this clinical problem is estimated at 1.75 million disability adjusted life years lost and represents 1.4% of the total healthcare burden in established market economies.[1,4] People suffering a hip fracture have a mean age of 83 years and two-thirds are women.[2] They suffer a 30-day mortality of 7% and experience a persistent reduction in their health-related quality-of-life similar to that of a patient with Parkinson's disease or multiple sclerosis.[5]

6.2 Need for a Trials Platform

The National Institute for Health and Care Excellence (NICE) updated the guidance for hip fracture management in May 2017.[6] The committee was unable to offer a recommendation in several areas of care for patients with hip fractures. NICE[7] and similar bodies around the world have made many research recommendations exploring the clinical and cost-effectiveness of treatments for this patient group. With this substantial burden of disease, and uncertainty in the clinical and cost-effectiveness of existing treatments, there is a pressing need to definitively test new interventions to improve outcomes for patients with hip fracture.

Extensive experience has been developed in the UK in the conduct of multicentre randomised trials in hip fracture. A series of related but independent trials have been planned and delivered under the WHiTE programme of work.[8–13]

In order to be able to test multiple components of the care pathway at pace and at scale, it is necessary to leverage the efficiencies that can be made within the overarching structure of a single Platform and Master Protocol. In addition, this approach improves the clarity of the research proposal for potential participants and greatly reduces the burden of participation.

6.3 How does the existing literature support this proposal?

Recent international cohort and registry observational studies have demonstrated that clinical practice remains variable worldwide for patients with hip fractures.[14] This variation is present through the initial assessment of patients, surgical and peri-operative care, rehabilitation and secondary prevention of future fractures. There is a pressing need to extend and strengthen the evidence base throughout the pathway of care. The WHiTE trials platform offers the opportunity to test multiple interventions to improve patient outcomes throughout the care pathway using an established network of recruiting centres and efficient design methodology.

7 OBJECTIVES AND OUTCOME MEASURES

7.1 Objective

To set in place a research and governance infrastructure for the efficient delivery of a suite of randomised comparisons to improve the care of people with a hip fracture.

7.2 Outcomes

We will collect a common outcome dataset (Table 1) across all randomised comparisons at 4 months post-diagnosis of a hip fracture at a minimum. In addition, longer term outcomes will be collected using routinely collected data up until the last follow up time-point for the participant according to the randomised comparison(s) they are enrolled in.

Any other outcome collection will be described in full in the relevant appendix depending upon the nature of the randomised comparison(s) in which the participant has enrolled. Additionally for CTIMP arms, depending on the risk and status of the IMP, part of the objectives will be to collect safety endpoints, as determined by the risk assessment of that interventional arm.

Outcomes	Objectives	Outcome Measures	Timepoint(s)
Short-term outcomes	To compare health-related quality-of-life (HRQoL) between treatment groups	EuroQol 5 Dimensions 5 levels (EQ-5D-5L)	Baseline and at 4 months post-diagnosis of a hip fracture
	To compare mobility between treatment groups	modified New Mobility Score (mNMS)	Baseline and at 4 months post-diagnosis of a hip fracture
	To compare residential status between treatment groups	UK National Hip Fracture Database Residential Status	Baseline and at 4 months post-diagnosis of a hip fracture
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Long-term outcomes	To compare risk and pattern of complications between treatment groups	Bespoke diagnostic and procedural events within linked routinely collected databases	Up to final appendix-specific follow-up time-point

	To compare the healthcare and broader resource implications between treatment groups	Bespoke diagnostic and procedural events & healthcare contact reimbursement data within linked routinely collected databases	Up to final appendix-specific follow-up time-point
	To compare mortality risk between treatment groups	Linked routinely collected registers of death events and attributed causes	Up to final appendix-specific follow-up time-point

Table 1: Common outcome dataset for the Platform

8 PLATFORM DESIGN

This is a platform framework, designed to efficiently deliver multiple randomised comparisons of interventions for older people with a hip fracture. All patients aged 60 years and over with a hip fracture presenting to the WHiTE recruitment centres will be considered for eligibility for each of the randomised comparisons. They will be offered the opportunity to take part in any or all of the randomised comparisons for which they are eligible. Comparisons may be contemporaneous or distributed throughout the treatment pathway. As new randomised comparisons are added to the WHiTE platform, they will be assigned a unique numeric identifier (i.e. WHiTE 11, WHiTE 12, etc) and a separate appendix to this Master Protocol will be created. Each comparison will be added as a substantial amendment to the platform. Amendments to the Master Protocol will carry through to each of the randomised comparisons; amendments to each randomised comparison will only be relevant to that appendix.

Eligibility for each comparison will be assessed against the specific criteria described in the relevant appendix. Interventions may be simple, complex or multimodal, e.g. investigational medicinal products, surgical interventions or care pathways; delivered at any stage along the diagnostic, treatment and rehabilitation pathway. Figure 1 provides an illustration of flow through the platform with four hypothetical comparisons (A-D).

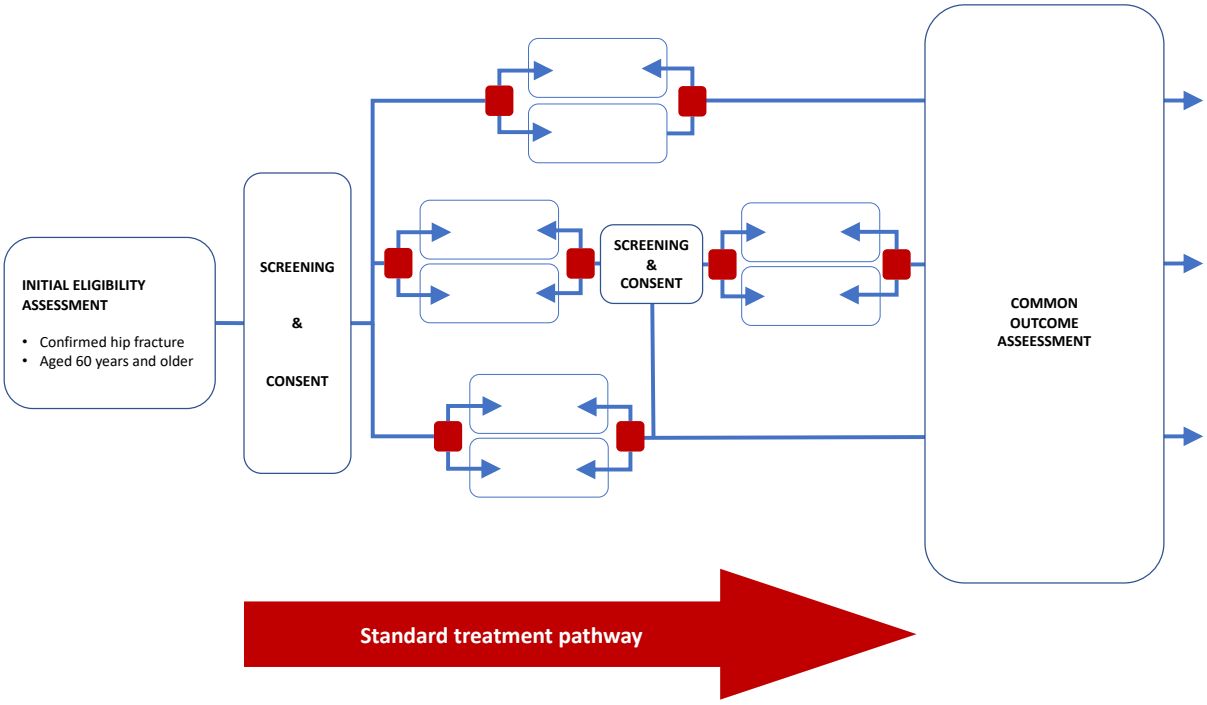

Figure 1: Platform summary. Key: 1/2 are randomly assigned treatment alternatives for clinical treatments A, B, C & D

9 RECRUITMENT CENTRES

9.1 Selection of centres

Each recruitment centre will routinely provide care for patients with hip fracture. Each centre will have a written standardised care pathway for hip fracture patients, a named medically qualified person who will take responsibility for the overall platform as the Principal Investigator (PI), appropriately trained research

staff, appropriate capacity for data collection and be willing to screen all eligible patients. Centres that agree to take part in the platform will not be obliged to participate in all randomised comparisons. Instead they will be selected to perform randomised interventions based upon their ability to deliver the requirements of each specific randomised comparison appendix. A separate randomised comparison-specific recruitment centre selection proforma will be created for each randomised comparison.

A local lead investigator may be identified and selected at sites to have delegated responsibility for the oversight of a particular randomised comparison by the platform PI if a health care professional with a certain speciality would be more suitable for that randomised intervention. This local lead investigator would therefore take on PI duties for that randomised comparison.

9.2 Recruitment centre training

Each recruitment centre will be required to have a PI, one research associate and any relevant additional staff (e.g. pharmacist, physiotherapist if appropriate for the intervention) to participate in WHiTE training prior to opening to recruitment. This may be in the form of a face-to-face site initiation training or participation in an appropriate remote training session. It will be the responsibility of those who attend the training to disseminate the training to other recruitment centre personnel. Once recruitment centre training has been completed, the members of staff who have completed the training should be added to the training log and signed off by the local PI. At least one member of staff from each recruitment centre who will be carrying out data entry will be required to be present for the electronic data collection training aspect of the training and complete a dummy data exercise in order to gain access to the database prior to recruitment centre activation.

All PIs and co-investigators will be expected to provide evidence of GCP training prior to participation in the Platform and the appended comparisons.

10 PARTICIPANT IDENTIFICATION

10.1 Participants

All adults aged 60 years or over diagnosed with a hip fracture by the treating clinical team at the recruitment centres will be potentially eligible for the Platform. Broad eligibility criteria will ensure that the results of the research can readily be generalised to the wider patient population. Eligibility for each of the randomised comparisons will also be assessed against the eligibility criteria described in the relevant appendices.

10.2 Inclusion Criteria

- Adults aged 60 years and over with a hip fracture

Further specific inclusion criteria for each of the randomised comparisons will be available in each of their appendices.

10.3 Exclusion Criteria

- Previous participation in the same randomised comparison
- A second hip fracture (other side) while the patient is still enrolled in the Platform following their first hip fracture. [Enrolment for a second time to the White Platform based on a second fracture

is possible once all final follow-up time-points for the comparisons they participate in with their first injury have ended]

Further specific exclusion criteria for each of the randomised comparisons will be available in each of their appendices.

11 PROCEDURES

11.1 Recruitment

The clinical care team will assess new patients for their initial eligibility and their capacity to consent. They will then notify a member of staff delegated to conduct screening of any potentially eligible patients to determine eligibility for any of the randomised comparisons.

11.2 Standard operative procedures

Participants will usually be assessed in the Emergency Department. Diagnosis of a hip fracture will be confirmed by a plain radiograph, as per routine clinical care. Routine investigations, anaesthetic assessment, antibiotic and venous thromboembolic prophylaxis will be used as per local policy. The details of the anaesthetic technique and the surgical repair/replacement will be left to the discretion of the clinical team as per their normal clinical practice. Details of the surgical procedure will be recorded in the CRF. The local multi-disciplinary team will be responsible for delivering rehabilitation and managing onward referral and discharge planning as per usual practice, according to local care pathways. Any changes to the standard operating procedures required by the randomised comparisons will be described in the relevant appendix.

11.3 Screening and Eligibility Assessment

A member of the clinical team, with routine access to the patient's personal data, will screen each patient to determine their age and diagnosis of a hip fracture. All potentially eligible patients will be screened and assessed for eligibility for entry into each randomised comparison by a member of staff delegated to conduct screening. Pre-enrolment eligibility checks will be carried out to ensure that participants are not enrolled in error. Screening logs will be kept at each recruitment centre to determine the number of patients assessed for eligibility into each comparison and reasons for any exclusion. The screening logs will contain non-identifiable information such as the age, sex, date of diagnosis which will allow for an assessment of the generalisability of the research.

Some randomised comparisons will depend upon eligibility criteria which can be assessed at the time of initial diagnosis of the hip fracture, for example age, sex, fracture classification. However, the eligibility for other randomised comparisons may be dependent upon earlier randomisations (i.e. allocation to a specific treatment arm) or on patient characteristics which only become apparent later in the treatment pathway, for example post-operative delirium. In these circumstances, additional eligibility assessments will be made at later stages of a participant's journey through the Platform.

The eligibility checklists will be completed by the member of staff carrying out the screening and approved by an appropriately trained clinician to confirm eligibility of the patient. Inclusion of the participants in each of the randomised comparisons will be recorded in the clinical notes by the staff member. Protocol waivers are not permitted.

11.4 Informed Consent

11.4.1 Timing

Once eligibility for any of the randomised comparisons has been confirmed, informed consent will be sought. For those participants who are eligible for further randomised comparisons later in the treatment pathway, additional consent discussions will be undertaken as appropriate. The processes, as described below, will be followed by a delegated member of the research team who has received platform specific training.

11.4.2 Capacity

Patients will be presumed to have capacity unless established otherwise and the default will be to seek prospective individual consent from every patient. However, patients with a hip fracture are a clinical priority for urgent operative care, are in pain and have often received opiate analgesia. It is therefore understandable that the majority of patients find the initial period of their treatment confusing and disorientating. Similarly, patients' next-of-kin, carers and friends are often anxious at this time and may have difficulty in weighing the large amounts of information that they are given about the injury and plan for treatment.

In this emergency situation, the focus is on obtaining consent for treatment (where possible) and on informing the patient and any next-of-kin about immediate clinical care. It is often not possible for the patient or relative/carer to review documentation about the Platform and relevant comparisons, weigh the information and communicate an informed decision about whether they would wish to participate. The clinical team will make a judgement about the amount and complexity of the information that the participant is able to understand and retain on an individual basis and whether individuals have capacity to consent or whether to approach a personal or professional contact on their behalf. For guidance on the assessment of capacity in non-CTIMPs, recruitment centres in England and Wales should refer to guidance from the Mental Capacity Act 2005 to assess the patient's decision-making capacity, those in Scotland should refer to that of the Adults with Incapacity (Scotland) Act 2000 and those in Northern Ireland to the Mental Capacity Act 2016 (Northern Ireland). For CTIMPs recruitment centres should refer to the Medicines for Human Use (Clinical Trials) Regulations for guidance. The consent procedure for the Platform will be informed by the capacity assessment to guide the proper approach to consenting to the research and who would be deemed most suitable to approach about this, as detailed below.

Best efforts will be made to involve participants who, temporarily or permanently, lack capacity in the decision to be involved in the Platform. Appropriate information will be communicated to the patient and updated as their understanding changes. At all times the research team will act in accordance with the participants' best interests. Any new information that arises during the Platform that may affect participants' willingness to take part will be reviewed by the Oversight Committees; if necessary, this will be communicated to all participants and a revised consent form completed.

11.4.3 Distinction between enrolling participants into clinical trial of an investigational medical product (CTIMP) and non-CTIMP comparisons

The legal basis for enrolling patients into research studies, who lack capacity at the time of entry into the Platform, varies across the four nations of the United Kingdom and depending upon the nature of the randomised comparisons for which the patient is being considered. For CTIMPs the UK Medicines for Human Use (Clinical Trials) Regulations 2004 is the guiding legislation. For non-CTIMPs:

- *England & Wales:* Mental Capacity Act 2005.
- *Northern Ireland:* Mental Capacity Act 2016 (Northern Ireland).
- *Scotland:* Adults with Incapacity (Scotland) Act 2000.

We recognise that there will be three groups of patients at enrolment:

A. Those who might participate only in comparisons not involving IMPs.
B. Those who might participate in a combination of comparisons, some involving IMPs and others not.
C. Those who might participate only in comparisons involving IMPs.

For participants in group A we will follow the procedures for non-CTIMPs; for those in groups B & C, we will follow the procedures for CTIMPs. We set out below the approach to the appropriate enrolment of participants in each of these circumstances in each of the devolved nations.

11.4.4 Patients enrolling into at least one CTIMP comparison

Where an eligible patient lacks capacity at the time of enrolment, we will act in accordance with the UK Medicines for Human Use (Clinical Trials) Regulations and seek a Legal Representative who can be asked to give consent on behalf of an adult who lacks capacity to do so themselves.

Where a Personal Legal Representative is available, they will be provided with the research information. A Personal Legal Representative is defined as follows, depending on the relevant nation:

- *England, Wales and Northern Ireland*: a person not connected with the conduct of the Platform who is suitable to act as the legal representative by virtue of their relationship with the adult and is available and willing to do so.
- *Scotland: 1)* the adult's guardian or, if not appointed, *2)* their welfare attorney, or if not appointed, then *3)* the adult's nearest relative.

The Personal Legal Representative will be given the opportunity to ask questions and discuss the Platform and relevant comparisons, after which their consent to enter the patient will be sought. Where a Personal Legal Representative is not available, then a Professional Legal Representative will be identified to advise the research team. A Professional Legal Representative must be independent of the Platform and can be either:

a) a doctor primarily responsible for the patient's medical treatment, or
b) a person nominated by the relevant healthcare provider.

The Personal/Professional Legal Representative will be asked to provide written consent on behalf of the participant after being told that they are free to decide whether they wish to make this decision or not, and to consider what the participant would want, and to set aside their own personal views when making this decision. The Legal Representative will be given sufficient information, in an understandable form, about the WHiTE platform and the randomised comparisons to ensure that they can make an informed decision.

11.4.5 Patients enrolling only into non-CTIMP comparisons

Where an eligible patient lacks capacity at the time of enrolment, we will follow a process approved by the relevant research ethics committee and act in accordance with:

- *England & Wales:* section 32(9) of the Mental Capacity Act 2005
- *Northern Ireland:* sections 135 & 136 of the Mental Capacity Act 2016 (Northern Ireland)
- *Scotland*: Adults with Incapacity (Scotland) Act 2000.

In England, Wales and Northern Ireland

We will seek a consultee, or nominated person in Northern Ireland, for simplicity hence described as a consultee. The consultee will be asked to advise the research team of any information regarding the patient that might indicate their unwillingness to enter the Platform.

A Personal Consultee is a person who is:

- engaged in caring for the participant (not professionally or for payment) or is interested in his/her welfare, and
- is prepared to be consulted.

Where a Personal Consultee is available, they will be provided with the relevant information. The Personal Consultee will be given the opportunity to ask questions and discuss the Platform, after which their advice will be recorded. Where a Personal Consultee is not available then a Nominated Consultee will be identified to advise the research team.

The Nominated Consultee will usually be the patient's treating clinician but may also be another healthcare professional, who must be independent of the Platform. If that surgeon (or healthcare professional) is a member of the research team, another independent healthcare professional will be identified. This will be a professional whom the local research team deems appropriately qualified. The role of the Nominated Consultee will initially be introduced by the local PI to clinical professionals undertaking the role of Nominated Consultee. The potential Nominated Consultees will be provided with a copy of the Master Protocol and relevant appendix and the current prospective patient information sheet. This will be done at each recruitment centre upon beginning of the Platform and as new members join the clinical team. Prior to enrolment of a participant, the Nominated Consultee will be asked to advise the research team on whether the patient should participate in the Platform; this will be prospectively recorded during the electronic randomisation process. Thereafter, at the first appropriate opportunity when the clinical situation allows, the Nominated Consultee will provide sign off on the recorded declaration which includes the date of their declaration.

In Scotland

We will seek 1) the patient's guardian if appointed or 2) their welfare attorney, or if not appointed then 3) the adult's nearest relative, for their consent to enter the patient into the Platform (this person is hereafter referred to as a Deputy). They will be given sufficient information, in an understandable form, about the WHiTE platform and the randomised comparisons and the opportunity to ask questions and discuss the research to ensure that they can make an informed decision. They will be informed that they are free to decide whether they wish to make this decision or not, and to consider what the participant would want, and to set aside their own personal views when making this decision before being asked to provide written consent.

11.4.6 Initiation of Platform procedures

All procedures including randomisation, safety reporting, data collection, including linkage to routine NHS datasets, will commence as soon as consent or a declaration from a Consultee/Nominated Person/Deputy has been obtained. For those participants who are unable to self-report, the outcome questionnaire may be proxy-reported by an appropriate individual.

11.4.7 Recovery of capacity

At the first appropriate time when the participant has regained capacity, the research associate will provide the participant with the research information. The participant will be given the opportunity to ask questions and discuss the research with their family and carers for as long as they require.

For Non-CTIMPS, participants as described under group A (11.4.3) who regain capacity, will be informed about the study and their consent for continuation on the Platform will be sought. For CTIMPS, those participants as described under group B or C (11.4.3) who regain capacity, will be informed about their participation in the study and provided with information about the research. In both circumstances, if the participant does not wish to complete Platform procedures they will be given the opportunity to decline to continue with the Platform follow-up; they will be asked if they consent to the research team using routinely collected data through the data sharing described in this Master Protocol and relevant appendices. Alternatively, the participant can choose to withdraw completely.

For those participants who did not prospectively consent and had a Professional Legal Representative, guardian/welfare attorney/nearest relative consent, or a Nominated Consultee/Nominated Person declare, on their behalf and who still lack capacity after their treatment, every effort will be made to contact a family member or individual who knows the participant. This individual will be asked if they would be happy to assist in the proxy completion of the questionnaires normally presented to the participant. If no such individual can be identified, the participant will remain in the Platform. Under these circumstances, the local research team will contact the last known carer for the participant to obtain relevant baseline data.

On rare occasions, participants, who were enrolled in the Platform after advice was given by a Consultee/Nominated Person, may be discharged prior to being approached about providing consent. Similarly, some participants who had been enrolled after consent from a Legal Representative or guardian/welfare attorney/nearest relative may be discharged before being approached about the Platform. If this happens, the recruiting centre team will make every effort to discuss the research with the participant at their next clinical follow-up appointment. If the participant is not invited for any further routine clinical follow-ups, a cover letter and a participant information sheet will be sent in the post to the participant. The cover letter will inform the participant that a member of the research team will contact them via telephone to explain the research further. The letter also gives the participant the ability to opt out of receiving a phone call and taking part in the Platform by returning the opt out slip in a self-addressed envelope provided. When contacting the participant over the telephone, the research team will inform them that they have been enrolled into the Platform. For those participants who have been enrolled under the process for non-CTIMP comparisons, then informed consent will be sought. The participant's agreement will be recorded by the research associate on an informed consent checklist. For those participants who have been enrolled under the process for CTIMP comparisons, where consent has already been given, we will inform them of their participation, provide information about the research and give them to option of declining ongoing follow-up.

11.4.8 Subsequent Loss of Capacity

CTIMP comparisons

For those participants who consented to participate in a CTIMP comparison and lose capacity after this, consent will endure.

Non-CTIMP comparisons

For participants in England, Wales and Northern Ireland who subsequently lose capacity, every effort will be made to find a consultee/nominated person to answer the follow-up questions on their behalf.

For participants in Scotland the patient's guardian or welfare attorney, or if not appointed, the adult's nearest relative will be approached for consent to continue in the Platform. This deputy will be provided with an information sheet, and a written record will be made of their verbal declaration or consent as appropriate.

Where the consultee/nominated person does not wish to answer questions on their behalf, or where the deputy does not consent for the participant to participate in all future procedures; they can opt for the participant to remain in the Platform through ongoing sharing of their routinely collected personal data only. The sharing of their personal data will be as described in this Master Protocol. Their verbal agreement to this will be documented in the participant's medical notes.

11.4.9 Documentation of consent

Responsibility for recording and dating, verbal, electronic and/or written informed consent or advice will be with the investigator, or persons delegated by the investigator, who conducted the informed consent discussion. Delegated responsibility will be recorded on the site delegation log. Permission will be sought to inform the participant's GP of their participation in the research. Where possible, consent will be collected electronically, in rare cases a paper copy of the consent form can be used. In situations where a participant has capacity to consent but is unable to physically sign the consent form (e.g. due to a wrist injury or poor vision) a witness signature will be obtained from any individual present during the consent discussion, who is independent of the study team and whom the participant agrees is a suitable witness, to acknowledge that fully informed consent was obtained from the participant. Verbal consent/agreement will only be acceptable in those circumstances when participants are enrolled in non-IMP comparisons, as outlined in this Master Protocol and relevant appendices. The original electronic consent forms will be stored in the clinical trial database REDCap. The local team will provide the participant or legal representative with a copy of the form; depending on the preference of the participant/legal representative, this can be a paper copy or it can be a PDF file emailed directly to them. The local team will download and keep a PDF copy of the signed and dated consent form in the electronic Investigator Site File (eISF) at the recruitment centre. A copy will also be saved in the patient's medical notes.

11.5 Randomisation

Once participants have been entered into one or more randomised comparison(s), each participant will be randomised by the local research team via an online randomisation system. The allocation sequence(s) for each randomised comparison will be generated as described in detail in the relevant appendix. All centres will have access to an electronic device with web-access to a secure, 24-hour, web-based randomisation system. When a participant is randomised to an arm within a comparison, sufficient identifiable details will be logged on a secure, encrypted, web-based system provided by OCTRU. Basic information including

the participant initials, date of birth and eligibility checks will be entered. The participant will then receive a unique comparison-specific ID, they will have one per comparison in addition to an overall platform specific ID. The comparison IDs will be used on all appendix-related CRFs/communications, whilst the platform ID will be used by the programming team that will be used on all research documentation.

11.6 Blinding

For single-blinded comparisons, treatment allocation(s) will be recorded on the Baseline Case Report Form (CRF) and details about the intervention(s) received will be confirmed from the participant's medical record. For double-blinded comparisons, details of the treatment received will be collected from the participant's medicals record once the blind is broken at the end of that particular randomised comparison.

Further details about unblinding and code-breaking will be specified in each relevant appendix.

12 MEASUREMENTS

12.1 Timing of assessments

In this Platform, where we expect randomisations and allocations to treatments to be distributed with time, it is not possible to set the schedule of assessments against a single point of randomisation. Therefore, we define the time of a data collection episode against the diagnosis of a hip fracture. The point of diagnosis of the hip fracture is already identified in the Platform as it is the point at which initial eligibility assessments can begin.

12.2 Baseline data

After a patient is enrolled, a member of the local research team will approach the participant with a questionnaire which includes the (retrospective) pre-injury EQ-5D-5L, as well as questions about pre-injury resource use, residential and mobility status as well as relevant medical history. Hospital data regarding admission assessment and treatment, where appropriate, will be collected.

12.3 Common outcome data

The following common outcome dataset, including the core outcome measurement set[15,16] recommended for hip fracture research studies, will be collected for every participant enrolled into any of the comparisons within the Platform. Any additional outcome measurements relevant to individual comparisons will be described in the relevant comparison appendix.

12.3.1 Health-related quality-of-life

The primary outcome measure is the EuroQol EQ-5D-5L[17] index at 4-months post-diagnosis of a hip fracture. The EQ-5D-5L index is a validated measure of health-related quality of life, consisting of a five dimension health status classification system and a separate visual analogue scale.[18] Parsons et al demonstrated that the EQ-5D correlated strongly with a hip specific patient reported outcome measure (Oxford Hip Score), it has an independently determined minimally clinically important difference for hip fracture surgery and can be completed by patient proxies, such as relatives where the patients are unable to self-report.[13,19] Health status plateaus 4 months after hip fracture surgery and this is the time point where this measure is collected for the national hip fracture database. Assessing EQ-5D outcomes provides consistency with other clinical studies in this patient population.[12,19,20] EQ-5D is the recommended instrument in the UK core outcome set for hip fracture.[15]

EQ-5D-5L summary index values will be derived using the most up to date guidance from NICE;[21] currently this recommends mapping EQ-5D-5L descriptive system data onto the EQ-5D-3L valuation set using the Crosswalk Index Value Calculator.[22] The scale for this value set ranges from -0.594, indicating the worst possible heath state, to 1.0 and is anchored at 0 and 1.0 where these values indicate health states equivalent to death and full health respectively.

Using an anchor point for death, EQ-5D can be imputed for participants who do not survive to the primary time-point of 4 months which is particularly relevant in this population. Parsons et al modelled patient EQ-5D recovery trajectories after hip fracture surgery to assess the extent of any bias in 4-month outcomes by comparing complete case analysis, model-based projections and data imputation.[23] They showed that imputing a utility value of zero for death resulted in a very close approximation to the much more complex projection methods, which were highly dependent on early (pre 4-month) EQ-5D score data that would not be available in the setting of a trial.[23] The EQ-VAS will also be collected as part of the EQ-5D-5L questionnaire.

12.3.2 Mortality

Qualitative work with patients who sustain hip fractures identified mortality as an important metric.[15] This will be recorded by recruitment centres at discharge from the medical records, or at any point during follow-up. These data will be confirmed through linkages with Civil Registration (Deaths) (England & Wales), the General Register Office for Northern Ireland and the Statutory Registers of Births, Deaths, and Marriages in Scotland.

12.3.3 Mobility

The modified New Mobility Score (mNMS)[24] is a multi-component instrument that was developed originally to measure mobility in older adults with hip fracture in post-acute and community settings .[25] The instrument assesses ambulation inside the home, outside the home and whilst shopping. A score of 0-3 points is given for each component, resulting in a total score of 0-9 points.

12.3.4 Residential status

Changes in residential status provide a marker for the patients' independence through their hip fracture recovery and is one of the recommended core outcomes for trials assessing interventions in hip fractures.[15] It will be 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.

12.3.5 Complications

All expected serious adverse events related to the fracture, standard surgical procedure or the randomised non-IMP comparisons will be recorded as complications, unless they are more severe than expected in which case, they will be reportable SAEs. These events will be reported by recruitment centres as they become aware of events, as well as by participants, carers, or consultees. Complication events that are reported by participants (or their carers/consultees) in their follow-up questionnaires will be cross-checked by the central study staff by corroborating with either the treating staff at the recruitment centre at which the participants are recruited, or by their GP using the participant's medical notes.

12.3.6 Resource use

Clinical Reporting Forms will be designed to collect information on use of resources from medical records at the treating hospital during the initial inpatient stay, and post discharge for 4 months following diagnosis. Further resource use data will be collected from the participants to complement the medical records. Data collected will include hospital contacts related to the index fracture with hospitals other than the index treating sites, rehabilitation units and other care settings. Questions will also be asked about use of equipment and changes to the home, such as bath rails. To estimate burden on families, questions will be asked about private expenses with rehabilitation services, informal care, and loss of productivity.

Resources required to deliver the different types of treatment will be valued by liaising with local finance departments to review tariffs and health care resource groups. Further health and social care will be valued using national unit cost estimates for health and social care and reference costs from the department of health and social care[26] when available. Curtis and Burns also include unit estimates for equipment and home changes.[27] Informal care, productivity losses and lost income will be valued using Office of National Statistics or equivalent weekly average earnings estimates following a human capital approach. In sensitivity analyses assumptions will be varied to estimate robustness of results to different costing approaches.

12.4 Follow-up assessments

Follow-up contacts will be completed with the participant or a proxy either via telephone interviews by a member of the central research team, or through electronic means depending on the choice expressed by the participant or proxy at the time of consent/declaration. If the participant or proxy chooses telephone follow-ups, the research team will attempt to ring the participant, the personal consultee or carer four to five times over a period of two weeks and will leave a message if possible. If they are unable to reach them by telephone, the research team will post or email the questionnaire. If a response is not received within a period of two weeks, the team will check contact details with the GP and/or NHS Digital and send a further postal questionnaire. If, after another two weeks the questionnaire is not received, a final telephone call will be attempted. If the participant or proxy is unable to be contacted at this point, then these data will be considered missed. If there are further follow up time-points, the same attempts to contact them for the subsequent assessments will be made.

For electronic follow-up, emails and/or Short Messaging Service (SMS) messages with a personalised link to an electronic questionnaire will be sent out at the time a follow-up is due. Welcome messages post enrolment and anticipatory messages in advance of follow-up time-points will also be sent. Participants or proxies who do not complete the electronic questionnaires within a specified timeframe will receive two reminder emails and/or SMS messages, and if this does not elicit a response, the research team will attempt to contact them via telephone and follow the schedule as outlined above.

Where a Consultee/Nominated Person/Deputy or Legal Representative has declared that they feel the patient would wish to be involved or consented for them to enter the Platform, they will be contacted to provide follow-up data if the participant has continued loss of capacity. Where this person is no longer available or aware of the participant's quality of life and personal circumstances, an alternative carer will be approached.

Where a participant entered the Platform under a declaration from a professional and no person with knowledge of the participant's quality of life has been identified, we will contact the last known carer for

further follow-up. Carer contact details will be provided to the research team on Platform entry for this purpose.

Where the participant or carer cannot be contacted, or where complications are reported by a participant or carer, further information with regards to symptoms/treatment for those complications will be obtained from the participant's GP and/or the recruitment centre.

If all these methods of contact and data collection fail, then we will class the participant as a non-responder, or "lost to follow-up", for that time point.

At 4 months post-diagnosis of a hip fracture, the local research team will again review medical notes to collect further participant contacts with the treating hospital after initial discharge if required. These include additional re-admissions, outpatient and emergency contacts, and procedures and tests relating to the index fracture performed since diagnosis.

13 RANDOMISED COMPARISON DESIGNS

The additional details specific to each of the randomised comparison will be described in the relevant appendix.

14 WITHDRAWAL OF PARTICIPANTS

Participants may decline to continue to take part in the Platform, either from individual comparisons if they are recruited to multiple, or from the whole platform if they want to withdraw from it all, at any time without prejudice. A decision to decline consent or withdraw will not affect the standard of care the patient receives. Participants can withdraw their consent by contacting the research team, with the contact details provided on participant information materials and the Platform website. Participants who decline further contact can withdraw wholly from the Platform. In this case, a withdrawal form will be completed and thereafter no further data will be collected from that participant.

Participants will be given the option to continue their participation in the Platform, allowing the research team to use any routinely collected data through the data linkages described in the Master Protocol and any relevant appendices, and complete medical records checks, but to decline further additional data collection by the recruitment centre or central research teams.

If participants are enrolled in multiple comparisons, they may wish to withdraw from a particular comparison but continue in another. In this case, the same procedures will be followed as above but only for the comparison that they wish to withdraw from.

Upon withdrawal of the participant, any source data recorded up to the time of withdrawal will be collected and retained by the research team and included in the final analysis.

Once withdrawn, the participant will be advised to discuss their further care plan with the local clinical team.

15 SAFETY REPORTING

The overall reporting concept is stated here; full details are described in each comparison appendix.

In order that the safety reporting schedules for the WHiTE platform can be efficient, those requirements applied to CTIMP comparisons will be generalised across the entire platform.

15.1 Definitions

Table 2: Definitions in relation to safety when interventions/randomised comparisons involve an IMP

Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant. The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • results in death • is life-threatening • requires inpatient hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability/incapacity • consists of a congenital anomaly or birth defect. Other 'important medical events' may also be considered a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the Reference Safety Information for the medicinal product in question set out: • in the case of a product with a marketing authorisation, in the approved summary of product characteristics (SmPC) for that product

	• in the case of any other investigational medicinal product, in the approved investigator's brochure (IB) relating to the trial in question.

Table 3: Definitions in relation to safety when interventions/randomised comparisons do not involve an IMP

Adverse Event (AE)	Any untoward medical occurrence in a clinical trial participant.
Adverse Response/ Reaction (AR)	An untoward and unintended response related to a trial intervention/procedure.
Serious Adverse Event (SAE)	Any untoward medical occurrence that: • results in death, • is life-threatening, • requires hospitalisation or prolongation of existing hospitalisation, • results in persistent or significant disability or incapacity, • is a congenital anomaly or birth defect; or • is otherwise considered medically significant by the Investigator.
Suspected Unexpected Serious Adverse Response/ Reaction (SUSAR)	This term can be used in non-CTIMPs to describe a serious adverse response/reaction to a trial intervention/procedure, the nature or severity of which is not consistent with what is listed in the protocol or other applicable information as an expected event.

15.2 Assessment of Causality

The relationship of each adverse event to the interventions under investigation must be determined by a medically qualified individual according to the following definitions:

Related: The adverse event follows a reasonable temporal sequence from trial intervention administration. It cannot reasonably be attributed to any other cause:

- Definitely related: The AE is clearly related to the intervention
- Probably related: the AE is likely related to the intervention
- Possibly related: the AE may be related to the intervention

Unrelated: The adverse event is probably produced by the participant's clinical state or by other modes of therapy administered to the participant:

- Unlikely related: the AE is doubtfully related to the intervention
- Definitely unrelated: the AE is clearly not related to the intervention

15.3 Reporting Procedure for SAEs

15.3.1 Events exempt from reporting as SAEs

Across all the comparisons, SAEs which are related to and expected in the course of a hip fracture before, during and after the admission for a hip fracture including standard surgical procedures, will be exempt

from reporting as SAEs across all comparisons unless the event is considered related to an IMP intervention. SAEs related to IMPs will be subject to safety reporting as per the instructions further on in section 15.3. Instead, all other events must be reported on a 'Complications Case Report Form'. These are:

- Chest Infection/Pneumonia
- Urinary Tract Infection
- Cerebrovascular Accident
- Myocardial Infarction/Acute Coronary Syndrome
- Blood transfusion
- Acute Kidney Injury
- Pulmonary Embolism
- Deep Vein Thrombosis
- Additional surgery related to the hip fracture (including intra-operative)
- Damage to a nerve, tendon or blood vessel
- Dislocation
- Wound Infection
- Failure of fixation
- Non-union

Complications will be classified as:

- related systemic complications (venous thromboembolic phenomena, death, pneumonia, urinary tract infection, blood transfusion, acute cerebrovascular incident, acute cardiac event, acute kidney injury).
- related local complications (superficial/deep infection, non/mal union, dislocation, failure/removal/revision of implants including further surgery for intraoperative/ postoperative periprosthetic fracture, injury to adjacent structures such as nerves/tendons/blood vessels, other).

15.3.2 Reporting of death unrelated to the intervention

Death directly attributable to a pre-existing underlying condition and not deemed to be caused by the intervention should be reported on the Death Case Report Form.

15.3.3 Events which are subject to immediate SAE reporting

All serious events which are assessed as at least possibly related to the intervention must be reported on the SAE form which is generic for the platform but may have additional fields added to make an appendix specific SAE form, depending on the interventions being compared to ensure that causality is assessed for all interventions introduced in the platform.

Any serious adverse reaction deemed to be exempt from reporting as an SAE will be listed in each separate appendix with a justification as to why they are no longer reportable SAEs, and based on a risk proportionate approach and to a level of safety profile already documented for that intervention.

15.3.4 Procedure for immediate reporting of SAEs

The recruitment centre research team will complete a SAE report form for all reportable SAEs on the SAE reporting form on the clinical trial database within 24 hours of recruitment centre research team becoming aware of the event. The local PI or delegate (must be medically qualified) will perform the review and confirm assessment of causality and completeness of the SAE form.

Once a SAE is submitted on the clinical database, the database will automatically alert the central research team and the SAE will be reviewed centrally by the Nominated Person for the trial, as per OCTRU's SOPs.

15.3.5 Central review of the SAE

The Nominated Person for the Platform will review all incoming SAEs without delay and will raise any queries with the local PI until resolved. As there is no legal requirement to perform dual assessment of causality, the Nominated Person will only query the assessment if there is any concern regarding the judgement.

In the event that consensus is not reached between the PI and Nominated Person about assessment of causality this will be escalated to the CI for further discussion. If still no resolution is reached, both assessments will be taken into consideration.

15.4 Assessment of expectedness

15.4.1 CTIMP and non-CTIMP comparisons

For all comparisons, assessment of expectedness will **only** be performed centrally by the Nominated Person for the Platform. Expectedness of SARs will be determined according to the relevant and approved Reference Safety Information (RSI) section of the Investigators' Brochure/Summary of Product Characteristics described more fully in the relevant appendix. Expectedness of events related to interventions that are not IMPs will be assessed against the list of expected events in the relevant appendix.

15.5 Reporting of serious unexpected events to the MHRA and REC

15.5.1 SUSAR Reporting in appendices involving IMP interventions (CTIMPs)

All SUSARs will be reported by the central research team (sponsor delegate) to the relevant Competent Authority and to the REC and other parties as applicable and per instructions in the relevant OCTRU SOP. For fatal and life-threatening SUSARs, this will be done no later than 7 calendar days after the central research team is first aware of the reaction. Any additional relevant information will be reported within 8 calendar days of the initial report. All other SUSARs will be reported within 15 calendar days.

Treatment codes will be un-blinded for specific participants if applicable.

Principal Investigators will be informed of all SUSARs for the relevant IMP or other intervention for all studies with the same Sponsor, whether or not the event occurred in the Platform.

15.5.2 Reporting of Related and Unexpected Events in appendices involving only non-IMPs (non-CTIMPs)

A serious adverse event (SAE) will be reported to the South Central – Berkshire REC where the event has been assessed as related to the intervention but unexpected according to the list of expected events. Reports of related and unexpected SAEs will be submitted within 15 working days of the Chief Investigator becoming aware of the event, using the HRA report of serious adverse event form (see HRA website).

The trials unit will not be reporting these SAEs to the MHRA and other relevant Competent Authorities unless requested by the so named parties.

15.6 Development Safety Update Reports (DSUR)

For interventional comparisons involving IMPs, the CI or the IMP manufacturer (if relevant) will submit DSURs once a year throughout the randomised comparison, or on request, to the Competent Authority (MHRA in the UK), Ethics Committee, HRA (where required), and Sponsor.

As this platform will involve a number of appendices with their own start and stop date, some of which will have IMP comparisons and others will not, the central research team will prepare a separate DSUR for each relevant appendix with an end date as to when the appendix will end.

The first DSUR will start on the annual anniversary of the Clinical Trial Authorisation for the first appendix with any IMPs; as more appendices are added to the platform, each of these appendices (if relevant) will have their own DSUR using the date of authorisation for that appendix.

16 STATISTICS

16.1 Summary of Statistical Analyses for each Randomised Comparison

A fully detailed statistical analysis plan (SAP) will be prepared for each randomised comparison and finalised after review by the DSMC and POC prior to any final analysis data-lock. These analyses will be summarised in the relevant appendix. Any subsequent changes to the SAP will be justified in the final report. A summary of the statistical approaches for the common outcome dataset across the Platform is provided here.

Principal analyses will be based on the intention to treat (ITT) principle (i.e., participants with available data will be analysed as they were randomised regardless of treatment received). Further analyses of different populations (e.g., per-protocol or as treatment) may be undertaken as outlined in the relevant randomised comparison appendix.

Baseline demographic data will be summarised to check comparability between treatment arms. Standard statistical summaries and graphical plots will be used to present findings between treatment groups for the primary outcome measure and secondary outcome measures. The principal analyses will be supplemented where appropriate with sensitivity analyses. The main analytical methods will use mixed-effects models and analyses will adjust for stratification factors and important baseline covariates to maximise precision. Details of adjustment will be pre-specified in the relevant randomised comparison appendix and SAP. With regard to the common outcome set, the EQ-5D-5L[17] index score at four months will be analysed by calculating an adjusted treatment effect by using a mixed-effects linear model to compare the EQ-5D-5L[17] score at 4 months (with a zero value imputed for those who have died at this time point) between the treatment arms adjusting for stratification factors (as per the relevant randomised comparison, e.g. age, sex and cognitive impairment) as fixed effects, and including recruitment centre as a random effect to allow for heterogeneity in the response between recruitment centres. A sensitivity analysis of EQ-5D-5L[17] at 4 months with additional adjustment for the retrospective pre-injury baseline EQ-5D-5L[17] will be performed to enable the influence of this factor to be evaluated. Other sensitivity analyses will be fully described in the SAP for the relevant randomised comparison. Other common outcomes will be similarly analysed with logistic regression being used for binary data and linear regression for continuous data.

Complications and other adverse events will be summarised, and comparisons will be considered exploratory unless indicated otherwise within the specific comparison documentation (e.g. randomised comparison appendix and statistical analysis plan).

16.2 The Level of Statistical Significance

Each set of randomised comparison analyses conducted within the WHiTE platform will be evaluated separately in terms of statistical significance. The statistical significance will be assessed at 5% for two-sided tests and reported for p-values less than 5% (p values of less than 0.05).

16.3 Procedure for Accounting for Missing, Unused, and Spurious Data.

Missing data will be minimised by careful data management. Missing data will be described with reasons given where available; the number and percentage of individuals in the missing category will be presented by treatment group. All data collected on data collection forms will be used, since only essential data items will be collected.

Some outcome data are likely to be unavailable due to lack of individual data items, declining consent for further follow-up, or general loss-to-follow-up. Where possible, reasons for data 'missingness' will be ascertained and reported. The nature and pattern of the missingness will be carefully considered – including in particular the nature of the missingness and whether it can be treated as missing completely at random (MCAR). Although the primary outcome analysis is reasonably robust to MCAR, sensitivity analyses will be performed, as appropriate, by imputing missing data with additional sensitivity analyses undertaken to assess the underlying missing data assumptions and to investigate the robustness of the results. Any imputation techniques will be fully described in the Statistical Analysis Plan.

16.4 Procedures for Reporting any Deviation(s) from the Original Statistical Plan

Any changes/deviations from the original randomised comparison SAP will be described and justified in the SAP and/or in the final report, as appropriate.

17 HEALTH ECONOMICS

17.1 Summary of Health Economic Analyses for each Randomised Comparison

A detailed health economic analysis plan (HEAP) will be prepared for each randomised comparison where funding has been secured for a full health economic evaluation and finalised after review by the DSMC and POC prior to any final analysis data-lock. These analyses will be summarised in each relevant appendix. Any subsequent changes to the HEAP will be justified in the final report. A summary of the core economic evaluation approaches for the common outcome dataset across the Platform is provided here.

17.2 Description of health economic methods

The economic evaluation will express cost-effectiveness in terms of incremental cost per quality-adjusted life year (QALY) gained associated with the experimental intervention from a health service and personal social services perspective at 4 months post-diagnosis of a hip fracture. We will report health and social care resource use values and their associated economic costs between diagnosis and 4 months post-diagnosis of a hip fracture using data extracted from bespoke resource use clinical reporting forms designed for each randomised comparison. Fractures in this elderly population may burden their carers and it is possible that different treatment pathways will have different consequences on their families and friends. As such, we will also report separately private expenses, informal care, and productivity losses incurred in both groups for patients and carers.

Any missing costs and QALYs will be jointly imputed using multiple imputation chained equations. Cost and QALY estimates will be bootstrapped and adjusted for stratification variables (e.g., recruitment centre)

and other potential variables as per the SAP, such as stratification variables, age, sex and cognitive impairment, in secondary analyses. “All available” and “imputed” cost categories and QALY data, will be reported by treatment group in a cost-consequences framework. The key cost-effectiveness parameter will be the bootstrapped incremental net monetary benefit statistic (INMB) derived using the recommended[28] UK societal willingness to pay thresholds of £20,000 and £30,000 per QALY. The INMB estimates if society is willing to pay more for the health benefit (QALY gained) than the incremental cost of the intervention. Positive values indicate the intervention is cost-effective. Using cost-effectiveness acceptability curves, we will depict the probability of the interventions being cost-effective at a range of cost-effectiveness thresholds to illustrate the uncertainty around the adoption decision. In one-way sensitivity analyses and scenario analyses, we will vary methodological assumptions to gauge robustness of results.

18 Data linkage for routinely collected patient-level data

18.1 Concept

Individual participant consent will be obtained for two separate groups of linkages:

Firstly, participants will be asked for consent to access their patient-level routinely collected data captured by the various UK data warehouses that hold information, including diagnostic and procedural codes relevant to hospitalisations and/or outpatient attendances for patients treated in NHS hospitals in order to provide a measure of long-term outcomes and NHS resource use. The duration of this consent will be until the final follow up time-point of all the comparisons into which an individual participant has enrolled. Periodically, at convenient intervals for the ongoing analyses planned for each randomised comparison, we will request these records and mortality records for all consenting participants.

Secondly, participants will also be asked for consent to access patient-level routinely-collected data captured by the two ongoing national hip fracture audits in the UK. These audits collect additional baseline and early follow-up data which will be used to corroborate the platform dataset, especially where data are missing or participants have withdrawn from ongoing follow up but have given consent to access their personal routinely collected data.

For participants treated in England, linkages will be sought with the admitted patient care, emergency care, outpatient care and critical care datasets within the Hospital Episode Statistics (HES) database; in Northern Ireland the Acute Episode-based Activity Statistics (EAS); in Wales, the Patient Episode Database for Wales (PEDW) derived from the Admitted Patient Care dataset; in Scotland, The Scottish Morbidity Register – General/Acute Inpatient and Day Case (SMR01). In addition, linkages will also be sought with the relevant registers of deaths and the causes of deaths in each jurisdiction. Civil Registration (deaths) provides a complete register of date and cause of death in England and Wales and is administered by NHS Digital; the General Register Office for Northern Ireland records deaths in this jurisdiction; the Statutory Registers of Births, Deaths and Marriages in Scotland is administered by the National Records of Scotland.

For participants in England, Wales and Northern Ireland linkages will be sought with The National Hip Fracture Database (NHFD).[2] Data include patients’ characteristics, fracture pattern, surgical interventions and measures of process such as time to theatre. These details are typically collected by specialist nurses within each hospital who provide continuity of care to patients with hip fractures and manage submissions to the NHFD. Linkages will also be requested from the National Joint Registry (NJR), which is a mandatory

registry that collects data on total hip replacement, including those performed for hip fracture in England, Wales and Northern Ireland. Baseline demographic data, details of the operative procedure and implant are recorded at hospitals and reported via a web-based portal. Revision outcomes are captured with revision defined as any operation where an implant is added, removed or modified.

For participants in Scotland, linkages will be sought with The Scottish Hip Fracture Audit.[29] Similar data to those collected in the NHFD are collected and submitted by specialist nurses from patients with a hip fracture.

For the purposes of the data analyses the research team will only process linked, de-identified data. In order that this dataset can be created, identifiable data will be provided to each data controller for the purpose of the linkage. A bespoke cohort will be generated from the Platform database and sent to each data controller containing participant health service number, date of birth, sex and postcode as well as a unique identifier for linkage. The trusted third parties will link the cohort to the relevant civil register of deaths and administrative databases in their jurisdiction and return the relevant variables.

18.2 Data flows

A summary of the data flows is presented in the below diagram (Figure 2).

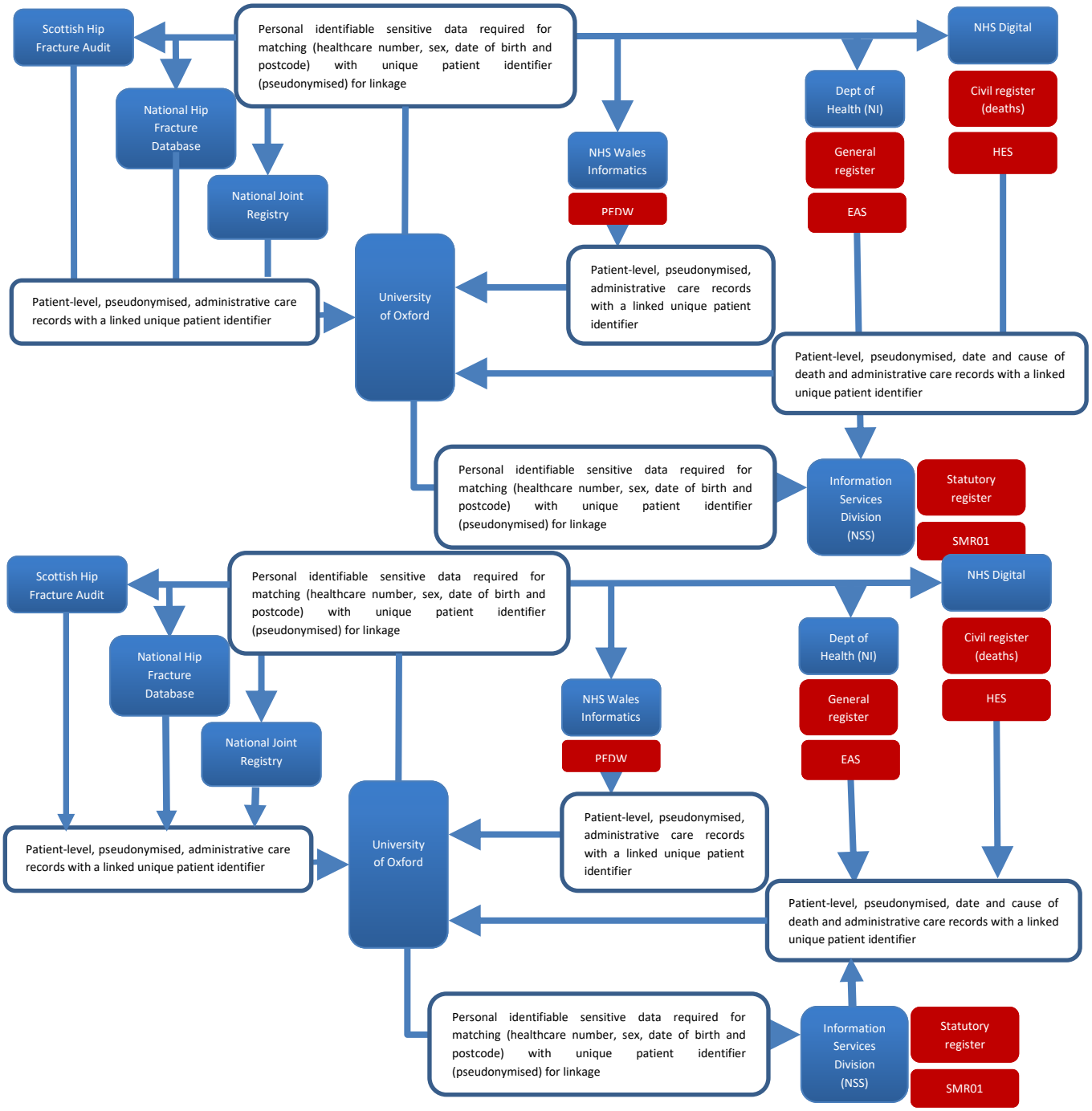

Figure 2: Data flow diagram for all participants in the WHiTE Trials Platform

Identifiable data from the bespoke cohort will be provided to NHFD, Scottish Hip Fracture Audit (SHFA) and NJR for data linkage. University of Oxford will send health service number, date of birth, sex and postcode as well as a unique patient identifier (de-identified) for linkage. The legal basis for the NHFD to collect personal data is Section 251 of the NHS Act 2006 (CAG 8-03(PR11)/2013). The existing approval for the NHFD is in place for the duration of the audit providing there is no deviation from the terms of the

original approval; annual reviews are submitted each year to confirm compliance with the conditions of support. The legal basis for the SHFA to collect personal data is the General Data Protection Regulation (article 6(1)e - public interest). The legal basis for collection and analysis of personal data by the NJR is under common law and a combination of consent (reasonable expectations) and Section 251 of the NHS Act 2006 (CAG 8-03(PR11)/2013), the GDPR legal basis is article 6(1)e (public task) and 9(2)j (statistics and archiving). The legal basis for the University of Oxford to collect and transfer these personal data to the trusted third parties is participant consent (section 251 of the NHS Act 2006 and the Health Service (Control of Patient Information) Regulations 2002.).

Identifiable data from the bespoke cohort will be provided to NHS Digital, Dept. of Health (Northern Ireland) and NHS Wales Informatics Service for data linkage. University of Oxford will send the health service number, date of birth, sex and postcode as well as a unique patient identifier (de-identified) for linkage. The legal basis for the University of Oxford to collect and transfer these personal data to the trusted third parties is participant consent (section 261.2(c) of the Health and Social Care Act 2012).

NHS Digital will link Civil Registration (deaths) date and cause of death and HES data with the unique identifier. University of Oxford will receive from NHS Digital patient-level de-identified data only, i.e. the linked date and cause of death as well as HES data with the unique patient identifier. The legal basis for University of Oxford to receive and process data from NHS Digital is Articles 6 and 9 of the General Data Protection Regulations (GDPR).

Department of Health (Northern Ireland) will link General Register Office for Northern Ireland date and cause of death and EAS data with the unique identifier. University of Oxford will receive from Department of Health (Northern Ireland) patient-level de-identified data only, i.e. the linked date and cause of death as well as EAS data with the unique patient identifier. The legal basis for University of Oxford to receive data from NHS Digital is the Health and Social Care Act 2012.

NHS Wales Informatics Services will link PEDW data with the unique identifier. University of Oxford will receive from NHS Wales Informatics Services patient-level de-identified data only, i.e. the linked PEDW data with the unique patient identifier. The legal basis for University of Oxford to receive data from NHS Digital is the Health and Social Care Act 2012.

University of Oxford will aggregate these datasets for each participant using the unique patient identifier (de-identified) to create a research dataset for the processing purposes described within the statistical analyses contained within the master protocol.

18.3 Description of analysis methods

Linked routinely collected data will be received at episode level (period of time a patient is under the care of a consultant), from which spells of continuous care will be built and combined with mortality data from the national registries.

For each randomised comparison, statistical models will be estimated to investigate the association between treatment and categorical variables based upon events identified through International Classification of Diseases (ICD; diagnostic), Office of Population Censuses and Surveys (OPCS; procedure) codes, and deaths. The specific events of interest will be described in each of the appendices.

Where applicable, sensitivity analyses will be conducted comparing the in-trial analyses based upon bespoke CRF data with those based on the linked administrative data to provide context for the long-term analyses.

In addition, patient-level profiles of resource use associated with linked hospital episodes encompassing inpatient admissions, outpatient visits and emergency department attendances will be costed using NHS Reference Costs.

19 DATA MANAGEMENT

The general data management principles of the Platform are summarised here with details fully described in the Platform Master Data Management Plan with appendices for each specific randomised comparison. Efficiencies will be made by the production of a common library of CRFs for the data collection to the randomised comparisons, augmented by additional forms for any extra measurements described in the appendices.

The Oxford Clinical Trials Research Unit at the University of Oxford will facilitate the Platform database containing demographic and outcome data for each of the participants.

Personal data collected during the Platform will be handled and stored in accordance with the University of Oxford data protection policies as well as the General Data Protection Regulation and Data Protection Act 2018, which require data to be de-identified as soon as it is practical to do so.

19.1 Source Data

Source documents are where data are first recorded, and from which participants' CRF data are obtained. These can include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarised into the CRF), clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, audio and video recordings, correspondence and routinely collected hospital administrative records, national audits and national mortality registers. Source data definitions for each comparison are described in the relevant appendix.

Clinical Reporting Form entries, such as patient-reported outcome measures that are submitted directly to the recruitment centre or central research team, will be considered source data if the CRF is the site of the original recording (e.g. there is no other written or electronic record of data). All documents will be stored safely in confidential conditions. On all Platform-specific documents, other than the signed consent, the participant will be referred to by the participant number, not by name.

19.2 Access to Data and Data Processing

To ensure compliance with regulations, direct access will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit relevant monitoring, audits and inspections. The data submitted directly to the Sponsor via the clinical database (e.g. electronic patient reported outcomes) will also be made available to the recruitment centre.

The processing of the requested data will be carried out in the course of its legitimate activities by a University of Oxford research team. The data processing will be undertaken exclusively by a limited number of experienced members of the research team and will be carried out with appropriate safeguards for the rights and freedoms of the participants.

For the purposes of analyses, the research team will only process de-identified patient level data. Data required as evidence for publications will be appropriately processed including de-identification and suppression of fields with low data counts. Where possible, aggregated (rather than individual) data will be supplied.

19.3 Data Recording and Record Keeping

Data will be collected in electronic format with direct entry or upload onto the Platform database; including the collection of documentary evidence of consent or declaration. All data collected will be de-identified after the collection of the baseline demographic data and all participants given a unique participant number at the point of randomisation. Identifiable participant data will be held on a separate database and coded with a participant number to tag identifiable data to the outcome data. Personal identifiable data will not be disclosed to anyone other than staff involved in running the Platform.

19.4 Case Report forms

The CRFs will be designed by the Platform management team. Recruitment centres will enter data directly into an eCRF (electronic CRF) on the Platform database. At the follow up points, participants may complete a paper copy of the CRF. If so, this will be returned to the central research team by post and will be entered into the eCRF by relevant members of the research team. The paper copy will then be scanned and stored in the eTMF as per the CTU's SOPs.

The copies of eCRFs will be kept and stored at each recruitment centre in the eISF. The CRFs will be kept for the period described in the relevant appendix or as required by Trust regulations at each particular recruitment centre, whichever is longer.

Participant contact details will be entered directly into a secure online database with access provided to team members with a demonstrated need to do so.

19.5 Databases

The data collected from participants will be entered in de-identified form in the Platform database.

The databases will be set up by a computer programmer and all specifications agreed between the computer programmer, statistician and manager and other relevant members of the research team. REDCap (Research Electronic Data Capture)[30,31] is a secure, web-based application designed to support data capture for research studies, providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources. This will be used for data collection in the Platform. Wherever possible, data will be entered directly into the database by recruitment centre staff or participants. All data entered will be encrypted in transit between the client and server. All electronic information will be held on servers located in access-controlled server rooms at the University of Oxford. The data will be entered into a GCP compliant data collection system and stored in a database on the secure server, accessible only to members of the research team based on their role within the Platform. The database and server are backed up to a secure location on a regular basis.

Due to the patient population in the Platform we appreciate that direct electronic capture of data will not always be possible, so any paper CRFs collected during the Platform will be entered into the database by

the local or central research team. The procedure for data entry will be documented in the data management plan.

19.6 Data security

NDORMS at the University of Oxford has a Data Security and Protection Toolkit (ODS CODE: EE133863-NDORMS-BHDG Publication Status: 18/19 Standard Met Date of Publication: 29/03/2019 /).

The Data Protection Act registration number is Z575783X for the University of Oxford. The policy document can be accessed through the link below:

https://www.admin.ox.ac.uk/councilsec/compliance/dataprotection/

The NDORMS data privacy and security notices can be found at:

https://www.ndorms.ox.ac.uk/information-security-policy

https://www.ndorms.ox.ac.uk/about/data-privacy-notice

19.7 Processing of routinely collected data

Designated computer systems, noted on the NDORMS Asset Register, will be the storage location of the provided data. These will be physically and logically secured with access allowed to a limited number of nominated personnel. Confidential information will be handled with utmost care and will not be shared outside of the Platform for which it has been authorised.

Staff will work in a secure manner, including closing files containing sensitive data when not in use. Screens will be locked when leaving workstations for even a short break, requiring a secure password to reactivate. Physical locks will also be used to prevent unauthorised access to secure areas. Measures such as physically securing and encrypting data-holding machines and limiting access to them will mitigate many of the potential risks.

Periodically the Information Governance Lead will arrange to check log files on systems holding confidential information with results noted in the Asset Register. Audit procedures will be developed to ensure that they are minimally intrusive but draw on the full range of possible clues.

The Information Governance Lead will be notified immediately in the case of an actual or suspected breach, including but not limited to:

- Hardware theft
- Use of confidential data on unauthorised machines
- Discovery of confidential data in an unauthorised location
- Loss of data

The Information Governance Lead will notify other authorities as appropriate, including the Head of Department and incident reporting via the NHS Information Governance website (for breaches of NHS Digital data). Breaches will be recorded in the NDORMS Asset Register.

19.8 Data destruction and archiving

Participants' identifiable data will be securely destroyed 12 months after the completion of last randomised comparison for which they have been enrolled as per the applicable OCTRU SOPs and University of Oxford policies current at the time of data destruction.

Once the planned analyses have been completed the research data will be de-identified and archived as per OCTRU SOPs, University of Oxford and third-party data controller's policies. Data will be retained for 5 years, unless specified otherwise in a particular appendix. If a participant is co-enrolled into multiple comparisons, the archiving process for their data will not begin until the end of the comparison with the longest duration.

Consent forms will be downloaded by local recruitment centre teams before the end of the relevant comparisons for long term storage as part of the eISF (electronic Investigator Site File). They will be removed from the Platform database once relevant central monitoring activities of the forms has been completed and participants have completed their participation in all of the randomised comparisons that they were enrolled onto.

20 QUALITY ASSURANCE PROCEDURES

20.1 Risk assessment

Each randomised comparison will be conducted in accordance with the current approved Master Protocol and appendices, GCP, relevant regulations and standard operating procedures. There will be a risk assessment carried out overall for the Platform as well as separate risk assessments for each randomised comparison (CTIMP & Non-CTIMP). Risk assessments will be reviewed as necessary over the course of the Platform to reflect significant changes to the Master protocol and appendices or outcomes of monitoring activities. Ongoing risk assessment will continue as the Platform progresses to allow us to identify potential issues.

20.2 Quality control monitoring

The platform will only open to recruitment once OCTRU give the Green Light according to their processes. In addition, each appendix will only open as a substantial amendment and will also undergo a Green Light process.

Quality control procedures will be undertaken during the recruitment and data collection phases of the randomised comparison to ensure research is conducted, generated, recorded and reported in compliance with the Master Protocol and relevant appendices, GCP and ethics committee recommendations. The Lead Investigators and the Comparison Managers will develop all data management and monitoring plans and a risk-adapted approach will be taken for each comparison to ensure the appropriate level of monitoring takes place by the central research team .

20.3 Management and Oversight Committees

There are a number of committees involved with the oversight of the platform; they will all have oversight of both CTIMP and non-CTIMP studies.

20.3.1 Platform Management Group & Comparison Management Groups

The day-to-day management of each randomised comparison will be overseen by the Comparison Management Groups (CMG), who will meet monthly to assess progress. Their terms of reference will be agreed within a CMG charter for each group which will outline its roles and responsibilities. Each comparison will have its own Comparison Manager, who will be responsible for the training of research staff at each of the recruiting centres for that comparison. Oversight of the Comparison Managers will be provided by the Senior Trial Manager for the Platform. The core Platform Management Group (PMG) consists of the senior members of staff involved in the early design and set-up of the platform. Its terms of reference will be agreed within a PMG charter which will outline its roles and responsibilities. Statisticians, health economists and the information specialists will be closely involved in setting up data capture systems, design of databases and clinical reporting forms. Members of the core PMG will join each of the CMGs for the duration of that randomised comparison. Meetings of the PMG will be arranged on a bi-annual basis or more frequently if deemed necessary.

20.3.2 Platform Oversight Committee

The POC, which includes independent members, provides overall supervision of the Platform. Its terms of reference will be agreed within a POC charter which will outline its roles and responsibilities. Meetings of the POC will take place at least once a year when there are randomised comparisons open to recruitment and they will review the progress of each active comparison at that time. Additional meetings may also be arranged if required to discuss a specific randomised comparison at a timepoint that is separate to the annual overall POC meeting. An outline of the remit of the POC is to:

- monitor and supervise the progress of the Platform towards its interim and overall objectives
- review at regular intervals relevant information from other sources
- consider the recommendations of the DSMC
- inform the funding body on the progress of the Platform

20.3.3 Data and Safety Monitoring Committee

The DSMC is a group of independent experts external to the Platform who assess the progress, conduct, participant safety and, if required, critical endpoints of the Platform and the appended comparisons. The platform DSMC will adopt a DAMOCLES[32] based charter which defines its terms of reference and operation in relation to oversight of the Platform. They will review accruing data, summaries of the data presented by treatment group, and will assess the screening algorithm against the eligibility criteria for each randomised intervention. They will also consider emerging evidence from other related trials or research and review related SAEs that have been reported. They may advise the chair of the POC at any time if, in their view, the Platform or any randomised intervention should be stopped for ethical reasons, including concerns about participant safety. DSMC meetings will be held at least annually during which the committee will review all active comparisons. Full details including names will be included in the DSMC charter. As with the POC, additional meetings may also be arranged if required to discuss a specific randomised comparison at a timepoint that is separate to the annual overall platform DSMC meeting.

21 PROTOCOL DEVIATIONS

A deviation is a departure from the ethically approved protocol or other research document or process (e.g. consent process or administration of intervention) or from Good Clinical Practice (GCP) or any applicable regulatory requirements. Any deviations from the Master Protocol or randomised comparison appendices will be documented in a protocol deviation form and filed in the Platform Master File. All

important deviations will be reviewed by the central research team and if a serious breach is suspected, advice will be sought from the sponsor representative before it is escalated and reported to the relevant authorities.

22 SERIOUS BREACHES

The Medicines for Human Use (Clinical Trials) Regulations contain a requirement for the notification of "serious breaches" to the MHRA within 7 days of the Sponsor becoming aware of the breach.

A serious breach is defined as “A breach of GCP or the study protocol which is likely to affect to a significant degree

(a) the safety or physical or mental integrity of the subjects of the study; or

(b) the scientific value of the study”.

In the event that a serious breach is suspected the Sponsor must be contacted within 1 working day. In collaboration with the CI the serious breach will be reviewed by the Sponsor and, if appropriate, the Sponsor will report it to the REC committee, Regulatory authority and the relevant NHS host organisation within 7 calendar days.

23 ETHICAL AND REGULATORY CONSIDERATIONS

23.1 Declaration of Helsinki

The Investigator will ensure that the Platform is conducted in accordance with the principles of the Declaration of Helsinki.

23.2 Guidelines for Good Clinical Practice

The Investigator will ensure that the Platform is conducted in accordance with relevant regulations and within the principles of Good Clinical Practice.

23.3 Approvals

Following Sponsor approval, the Master protocol and relevant appendices, informed consent forms, participant information sheets and other participant-facing documents will be submitted to an appropriate Research Ethics Committee (REC), HRA, MHRA and host institution for written approval for each randomised comparison.

The Chief Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

23.4 Amendments

Each time a randomised comparison is added to the platform this will be submitted for consideration to the REC, HRA & MHRA as a substantial amendment to the Platform.

Individual appendices may require amendments that will not affect any other randomised comparisons, in this case the relevant approvals will only be sought for the affected appendix. A log of amendments to each randomised comparison will be kept within the relevant appendix protocol. A log of amendments in relation to any of the master documents will be kept in this master protocol document for tracking

purposes by the Platform management teams. Recruitment centre R&D departments will only need to approve amendments specific to the randomised comparisons in which they partake.

23.5 Other Ethical Considerations

As described earlier, the Platform will involve the participation of individuals who may lack capacity to provide consent themselves. Research teams at the recruiting centres all have extensive experience in working with patients who are unable to provide consent themselves. The research team also provide robust training to recruitment centres during Site Initiation Visits to ensure the correct consent pathway is followed; if patients are unable to consent then they will be enrolled into the Platform under advice from a Personal or Nominated Consultee and for CTIMPS from a legal representative. Following this, participants as described under group A (11.4.3) will be approached for their consent for continued participation into the Platform at the earliest opportunity if they regain capacity.

23.6 Reporting

23.6.1 Annual Progress Report (APR) to REC, HRA and Sponsor

The Chief Investigator shall submit once a year, or on request, an Annual Progress Report to the REC and HRA. The APR will report on all current appendices, and it will be clear which recruitment figures belong to which appendix of the platform. The date of anniversary will take into account the overall approval of the platform.

23.6.2 Progress Reports to funders and other parties

Progress reports to funders and other relevant parties will be done according to the terms and conditions stated in relevant agreements.

23.6.3 Reporting of results

Please refer to the section below, *Transparency in Research.*

23.7 Transparency in Research

The platform will be registered in EudraCT, a publicly accessible database, as part of obtaining approvals. In addition, the platform will also be registered in ISRCTN.

A protocol, SAP and HEAP will each be published prior to the conclusion of participant recruitment for each randomised intervention.

Results of each randomised comparison will be uploaded to the register within 12 months of the end of that comparison declared by the CI or their delegate.

Results from each comparison will be submitted for publication in a peer reviewed journal.

As it is anticipated that the Platform will be perpetual, results will not be entered onto EudraCT at the end of the first comparison as this will preclude further results being added; however, results will be entered once the platform is declared ended as a whole.

23.8 Declaring the end of each comparison and the end of the Platform

Each comparison, detailed as an appendix to the platform, will have a start and an end date. Any appendix approved with the initial platform approval will have its start date as the start of the overall approval of the platform. It will be clear from the Annual Progress Reports when each comparison will have ended.

The platform will be officially declared ended to the MHRA, REC and HRA when the last participant in any of the comparisons has reached their last follow-up time-point.

23.9 Participant Confidentiality

The Platform will comply with the General Data Protection Regulation (GDPR) and Data Protection Act 2018, which require data to be de-identified as soon as it is practical to do so. The processing of the personal data of participants will be minimised by making use of a unique participant number only on all documents and any electronic database(s), with the exception of the contact details, which will be kept in a secure database, separate from research data, and accessible only to the research staff who require this information for the follow up. All documents will be stored securely and only accessible by research staff and authorised personnel. The research staff will safeguard the privacy of participants' personal data.

23.10 Expenses and Benefits

Expenses may be paid to participants where research procedures are over and above the requirements of routine clinical care. Details of any incentives for participants will be described in the relevant appendix.

24 FINANCE AND INSURANCE

24.1 Funding

This platform is supported by the National Institute for Health and Care Research (NIHR) Oxford Biomedical Research Centre. Each randomised comparison will be funded individually, details of which will be specified in the relevant appendix. The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care.

24.2 Insurance

The Platform, including all appendices, will be sponsored by the University of Oxford. The University has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, at Lloyd's of London). NHS indemnity operates in respect of the clinical treatment that is provided.

24.3 Contractual arrangements

Appropriate contractual arrangements will be put in place with all third parties.

Data sharing agreements will be put in place with NHS Digital, NHS Wales Informatics Service, Department of Health (Northern Ireland), General Register Office of Northern Ireland and the University of Oxford to enable the data linkage required for the long term follow-up.

25 PUBLICATION POLICY

Outputs from the WHiTE platform will be prepared for each randomised comparison independently and specific details provided in each appendix.

Research outputs will be prepared by the Platform management team. No patient identifiable information will be contained in any form of dissemination of the results.

The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the Platform and the appended comparisons. Authors will acknowledge research funding. Authorship will be determined in accordance with the International Committee of Medical Journal Editors guidelines and other contributors will be acknowledged as per OCTRU SOPs.

The dissemination strategy will consist of three strands. The first will ensure that patients and the public are informed of the results; the second will engage practitioners and health-care providers, and the third will inform national guideline and policy makers.

25.1 Patients, patient advocacy groups & members of the public

Our patient representatives will lead dissemination to the patients and carers directly through their extensive network of patient advocacy organisations including the Royal Osteoporosis Society. They will help generate plain language summaries for patients and the public. These documents will be available in multiple mediums. Posters, abstracts and oral presentations will also be prepared with the PPI team for inclusion at any workshop or conference where relevant PPI is being discussed. In addition, to disseminate directly to participants, findings will be more widely available locally through posters in appropriate outpatient rooms and liaising with identified service user groups.

25.2 Health care providers

We will work through the Oxford NIHR BRC and the Oxford media team to maximise the reach of our press and publicity outputs from the Platform. We will cost free-to-access publications in the mainstream literature. The final results will be submitted for presentations at annual meetings including but not limited to the British Orthopaedic Association (BOA) and the Orthopaedic Trauma Society (OTS). Where appropriate, we will present the findings to the entire NHS via the NHS national electronic Library for Health (NHS Evidence). International ‘reach’ of our published research findings will be supplemented by presentations at high visibility meetings such as the OTA Annual Meeting (USA) and EFORT (Europe), and the Global Fragility Fracture Network (FFN) Congress. The FFN national and international networks will allow rapid worldwide dissemination of the results of these keenly anticipated research questions.

In addition, we are developing complementary systems incorporating non-traditional media. They have been very successful and have provided a means for rapid dissemination. We plan to expand this activity into additional subject-specific and general blogs.

Presentation slide decks of the funding, methodology, results and interpretation of the randomised comparisons will be created and made available to investigators for local/regional dissemination, and on the Platform website where appropriate.

25.3 National guidelines

We will use our established global network involvement to disseminate research findings. These include the NIHR Clinical Research Network, and specialist interest groups. We will alert the relevant NICE standing committee, and equivalent international bodies, to the results by notifying their surveillance teams.

26 THE GENERATION OF INTELLECTUAL PROPERTY

Ownership of IP generated by employees of the University of Oxford vests in the University. The University will ensure appropriate arrangements are in place as regards any new IP arising from the Platform.

27 REFERENCES

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