APPENDIX 11 to WHiTE Platform Master Protocol

World Hip Trauma Evaluation 11

Fix or Replace Undisplaced Intracapsular fractures Trial of Interventions (FRUITI)

This appendix must be read with the accompanying WHiTE Platform Master Protocol. This appendix describes only the additional details relevant to the conduct of this particular randomised comparison within the context of the overarching master protocol.

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Appendix 11 : World Hip Trauma Evaluation – FRUITI: Fix or Replace Undisplaced Intracapsular fractures Trial of Interventions

Short title: WHiTE 11- FRUITI

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We declare no conflicts of interest.

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1 APPENDIX AMENDMENT HISTORY

Amendment No.	Protocol Appendix Version No.	Date issued	Author(s) of changes	Details of Changes made
Initial submission	2.0	08Jan2021	Stephanie Wallis Elsa Marques	Clarification that protocol appendix must be used with Master Protocol. Addition of Health Economics analysis.
AM 02 (SA 01)	3.0	28Apr2021	Susan Dutton	Clarification of the sample size for the comparison.
AM 06 (SA 02)	4.0	14Oct2021	Xavier Griffin Mae Chester-Jones Amrita Athwal Stephanie Wallis	Update to Abbreviations List. Typographical updates to the synopsis table for clarification. Removal of SSPB from protocol due to lack of feasibility in light of COVID-19 restrictions; objective mobility at 6 weeks removed as a secondary objective. Corrections to references to the numbered sections of the master protocol. Updated the statistical methods section.
AM 06 (SA 02)	5.0	28Oct2021	Stephanie Wallis	Removal of 'at least' or 'minimum of' from proposed sample size wording.
AM14 (SA 05)	6.0	TBD	Amrita Athwal, David Keene, Xavier Griffin, Elisa Basso	Section 2 Change of Comparison Manager and contact details. Correction of reference to 'comparison' as opposed to 'trial' or 'study' throughout document where appropriate Section 4 and 7 Removal of a one-year quality adjusted life year (QALY) derive from the secondary objectives due to erroneous addition into the protocol appendix. Section 4 and 7. Alignment of wording of objectives for consistency with master protocol and clarification of distinguishing comparison-specific time-points from those that fall under the Platform common outcome set. Section 7 and 11.4 Update to outcome measure and statistical section to reflect the use of modified New Mobility Score.

				9.1 and flow chart Reference to overarching exclusion criteria in WHiTE Platform master protocol Section 9.6.1 Clarification that all 6 week data will be collected by telephone, online and /or postal method, rather than face to face in clinics. Section 10. Clarification added regarding justification for no requirement to collect AEs or unrelated SAEs.

2 KEY CONTACTS

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3 LAY SUMMARY

Every year around 70,000 people in the UK break their hip. Hip fractures are a common and very serious injury in older patients, similar in impact to a major stroke. We will investigate two treatments for one specific type of hip fracture. Currently, surgeons either repair the fracture with screws or remove and replace the broken piece of bone, but we do not know which is better for patients.

We will examine whether either fixing the broken bone or replacing the hip joint gives a better result for people 60 years and over with hip fractures from at least 40 hospitals across the UK. We want to look at how well people feel and how active they are following their fracture. We will also work out the cost of the two treatments – for the individual, for the health service and in terms of social support in the year following the fracture.

A pilot study in a smaller group of hospitals will look closely at our approach to this work – to check that enough people will want to take part in the full study. This will allow us to improve the study processes of the larger study before we get started. All the information from this pilot study will be included in the main study.

To compare the two treatments properly we need 878 people to take part. Over a third of people with a broken hip have memory problems, and as they can struggle to recover from this injury, we plan to include them in this study. If people agree to take part, they will be allocated using a process called randomisation which makes sure that the groups are similar and the comparison between the two treatments is fair. Before and after their operation all the patients will have the usual ward care, rehabilitation and follow up that is standard practice at their hospital.

We will ask patients about their health, pain, walking ability and other daily activities, as well as any complications and specific costs. Their answers will be collected at the outset, and at 6 weeks, 4 months and 1 year after confirmed diagnosis of their hip fracture, and the results from the two groups compared. A few questions will be asked each year for five years to find out about any longer-term effects. We will also ask people for their permission to use de-identified information, which means that it is unlikely that we can identify them from the records received, from national databases that are already being routinely collected.

This study falls under the WHITE Platform framework (see master protocol) and has been developed by a team of patient representatives, clinical experts in trauma orthopaedics, study management specialists, experienced statisticians and health economists. The Oxford Clinical Trials Research Unit, based at the University of Oxford, will assure the quality of the study. A monitoring committee of patient representatives and independent experts will oversee the progress and conduct of the study.

4 FRUITI SYNOPSIS

Comparison title	World Hip Trauma Evaluation – FRUITI: Fix or Replace Undisplaced Intracapsular fractures Trial of Interventions			
Short title	WHiTE 11 - FRUITI			
Registration	The comparison has been registered with the current controlled trials database under reference number; ISRCTN 28566489, CPMS ID 49158.			
Funder of FRUITI comparison	Department of Health – NIHR HTA Programme			
Design	Pragmatic, multicentre, two-arm randomised superiority comparison with parallel economic analyses follow-up to one year. Longer term follow-up will be achieved using patient reported outcomes and routinely collected data at 5 years.			
Participants	Adults aged 60 years and over with a hip fracture, who in the opinion of the treating surgeon may benefit from surgical treatment and meet the specific FRUITI eligibility criteria.			
Sample Size	878			
Comparison Duration	Total length of project: 107 months; set-up 5 months, 36 months recruitment, 60 months follow-up, 6 months analysis and report writing. Participants will be initially followed up for 12 months post-treatment. Long-term follow up will consist of annual participant follow-up and linkage to routinely collected healthcare databases for a further 4 years.			
Recruitment period	Estimated Mar 2021 – Apr 2024			
FRUITI Outcomes	**FRUITI Objectives**	**Instruments**	**Timepoint(s)**	
			Part of Platform common outcome set	**FRUITI-specific**
Primary	To compare health-related quality-of-life (HRQoL) between the treatment groups (internal fixation versus hip replacement)	EuroQol 5 Dimensions 5 levels (EQ-5D-5L)	**Participant:** Baseline and 4 months post-diagnosis of hip fracture	N/A
Secondary	1) To compare HRQoL between the treatment groups.	EuroQol 5 Dimensions 5 levels (EQ-5D-5L)	N/A	**Participant:** 6 weeks and 12 months post-diagnosis of a hip fracture Event-based (complication) reporting
	2) To compare mobility between the treatment groups	modified New Mobility Score (mNMS)	**Participant:** Baseline and 4 months post-	**Participant:** 6 weeks and 12 months post-

			diagnosis of a hip fracture	diagnosis of a hip fracture
	3) To compare pain between the treatment groups	Pain verbal rating scale (VRS)		**Participant: Baseline ,** 6 weeks , 4 and 12 months post-diagnosis of hip fracture
	4) To compare mortality risk between the treatment groups	Death notification CRF	4 months post-diagnosis of a hip fracture	12 months post-diagnosis of a hip fracture
	6) To compare residential status between the treatment groups	NHFD – residential status questions	**Participant:** Baseline and 4 months post-diagnosis of hip fracture	**Participant:** 6 weeks and 12 months post-diagnosis of hip fracture
	7) To compare the risk and pattern of complications between the treatment groups	Complications CRF, medical records check	**Participant:** 4 months post-diagnosis of hip fracture	**Participant:** 12 months post-diagnosis of hip fracture **Medical record:** discharge and 12 months post-diagnosis of a hip fracture
	8) To compare the healthcare and broader resource implications between the treatment groups	Review of hospital medical notes complemented by patient-completed resource use questionnaire	**Participant:** Baseline and 4 months post-diagnosis	**Participant:** 12 months post-diagnosis **Medical record:** Hospital discharge, and 12 months post-diagnosis of a hip fracture
Long-term (to be reported separately)	9) To investigate the difference in event risks for mortality and complications, as well as associated costs and health utilities between the treatment groups	EQ-5D, complications CRF Routinely collected data (RCD)	N/A	**Participant**: Yearly, up to 5 years post-diagnosis **RCD:** 5 years post-

				diagnosis of a hip fracture
Treatment	Arthroplasty: Hemiarthroplasty or total hip arthroplasty. Patient position, surgical approach, implant and surgical technique will be chosen by the operating surgeon.			
Comparator	Internal fixation: Sliding hip screw or cannulated screws. Fixation will be achieved using a technique and implant chosen by the operating surgeon.			

5 ABBREVIATIONS

AE	Adverse Event
ATOCP	Association of Trauma and Orthopaedic Chartered Physiotherapists
BOA	British Orthopaedic Association
CI	Chief Investigator
CLAHRC	Collaborations for Leadership in Applied Health Research and Care
TMF	Trial Master File
CMG	Comparison Management Group
CRF	Case Report Form
CT	Clinical Trials
CTA	Clinical Trials Administrator
DC	Data Clerk
DSMC	Data and Safety Monitoring Committee
EAS	Episode-based Activity Statistics
eCRF	Electronic Case Report Form
ED	Emergency Department
EFORT	European Federation of National Associations of Orthopaedics and Traumatology
eISF	Electronic Investigator Site File
EQ-5D-5L	EuroQol 5 Dimension 5 Level
GCP	Good Clinical Practice
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
HTA	Health Technology Assessment
ICD	International Statistical Classification of Diseases and Related Health Problems
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ITT	Intention to Treat
INMB	Incremental Net Monetary Benefit
MCAR	Missing completely at random
MCID	Minimal Clinically Important Difference

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 Research
NIHR BRC	NIHR Biomedical Research Centre
NIHR HTA	NIHR Health and Technology Assessment
mNMS	modified New Mobility Score
OA	Osteoarthrosis
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
PIL	Participant/ Patient Information Leaflet
POC	Platform Oversight Committee
QALY	Quality Adjusted Life Year
R&D	NHS Trust R&D Department
RCD	Routinely collected data
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SDV	Source Data Verification
SOP	Standard Operating Procedure
VRS	Verbal Rating Scale
WHiTE	World Hip Trauma Evaluation

6 BACKGROUND AND RATIONALE

6.1 What is the clinical problem being addressed?

Undisplaced, or minimally displaced intracapsular fractures represent approximately ten to fifteen per cent of all hip fractures.[1] In these fractures, the proximal femur is broken at the level of the neck, but the fracture fragments have remained anatomically aligned. Conventional treatment to stabilise the fracture with internal fixation is a quick procedure with minimal blood loss and has the key advantage of preserving the person's own hip joint.[2–4] However, healing can be unsuccessful in many patients, requiring revision surgery in up to 30% of cases.[3,4] For this reason hip replacement, where the fractured part of the bone is removed, may be preferred as the primary treatment. Hip replacement surgery eliminates the risk of fixation failure as the femoral neck is replaced. However, it is a more complex operation than internal fixation with very significant complications of its own, including a greater risk of infection, dislocation and periprosthetic fracture.[2]

6.2 How does the existing literature support this proposal?

Recent international cohort and registry observational studies have demonstrated that clinical practice remains variable worldwide for minimally displaced intracapsular fractures. These studies also suggest that adverse event risks, such as the need for further surgery, are higher amongst people treated with internal fixation. One small, underpowered, randomised controlled trial from China comparing the two interventions reported a four-fold difference in reoperation risks (hazard ratio 4.7, 95%CIs 1.0-21, p=0.049).[5] There was no evidence of a difference in patient-reported hip function at final follow-up but there was evidence of significant benefit of hip replacement in the early post-operative period. A similar small study conducted in Norway found similar risk ratios for reoperation but also a possible survival benefit in favour of hip replacement (control risk 36%, risk ratio 0.4 95%CIs -0.1-1.1).[6]

Overall, there is evidence of a trend for a difference in outcomes between the two interventions but no definitive trial which is generalisable to NHS practice from which to draw conclusions.

6.3 Need for this comparison

NICE updated the guidance for hip fracture management in May 2017.[7] The committee were unable to offer a recommendation for minimally displaced intracapsular hip fractures of either internal fixation or hip replacement due to the lack of sufficient evidence. A research recommendation exploring the clinical and cost-effectiveness of treatments for minimally displaced fractures was prioritised by the committee.

The Orthopaedic Trauma Society and Research Committee of the British Orthopaedic Association has also identified this research area as a priority. A working group at the Orthopaedic Trauma Society 2017 Conference (Annual Meeting, Warwick 2017) reached consensus for a definition of minimally displaced hip fractures for which true equipoise was identified across the Society which has been carried forward into this design.

With this substantial burden of disease, and uncertainty in the clinical and cost-effectiveness of the technologies, there is a need to definitively test if there is a difference in outcomes for adults aged 60 years and older with a minimally displaced intracapsular hip fracture treated with internal fixation or hip replacement.

7 OBJECTIVES AND OUTCOME MEASURES

7.1 Primary objective

To compare health-related quality-of-life (HRQoL) at 4 months post-diagnosis of a hip fracture between the treatment groups.

7.2 Secondary objectives

1. To compare HRQoL at 6 weeks and 12 months post-diagnosis of a hip fracture between the treatment groups.
2. To compare mobility at 6 weeks, 4 months and 12 months post-diagnosis of a hip fracture between the treatment groups
3. To compare pain at 6 weeks, 4 months and 12 months post-diagnosis of a hip fracture between the treatment groups.
4. To compare mortality risk within the first 12 months post-diagnosis of a hip fracture between the treatment groups.
5. To compare residential status at 6 weeks, 4 months and 12 months post-diagnosis of a hip fracture between the treatment groups.
6. To compare the risk and pattern of complications in the first 12 months post-diagnosis of a hip fracture between the treatment groups.
7. To compare the healthcare and broader resource implications over the first 12 months post-diagnosis of a hip fracture between the treatment groups.

7.3 Long-term objective

To compare the event risks for mortality, all-cause revision surgery (including conversion of fixation into replacement, operations for dislocation and infection) as well as associated costs and utilities between treatment groups over the first 5 years post-diagnosis of a hip fracture.

This objective will be reported separately from the main objectives to allow for primary outcomes to be disseminated in a timely manner.

7.4 Outcome Measures

The common outcome data described in the Master Protocol will be collected and augmented with additional data collection at 6 weeks, 4 and 12 months post-diagnosis. Health-related quality of life, complications and RCD will be collected annually for a further four years.

7.4.1 Primary

Health-related quality-of-life. The primary outcome measure is the EuroQol EQ-5D-5L[8] index at 4 months post diagnosis of a hip fracture.

7.4.2 Secondary

In addition to the common outcome instruments, described in the master protocol, a measure of pain will also be collected:

Pain: Participants or their proxy will report the pain verbal rating scale (VRS), a five responses ordinal scale (1-5) measuring pain;[12] responses are labelled “no pain,” “slight pain,” “moderate pain,” “severe pain,” and “unbearable pain” where 1 indicates “no pain” and 5 “unbearable pain”. It has been validated in

patients with hip fracture with good response rates, including from patients with cognitive impairment; it is reliable and sensitive in this patient group.

8 DESIGN

8.1 Concept

This is a randomised comparison embedded within the overarching WHiTE Platform testing clinical superiority between the treatment groups with a parallel economic analysis. The analyses are split into those reporting participant follow-up through to one year and long-term follow-up at five years post-diagnosis. The long-term analysis will depend upon routinely collected data and annually collected health-related quality of life data and will be reported separately. The primary outcome is the EQ-5D-5L[8] at four months post-diagnosis. Participants will be allocated using a 1:1 random allocation, stratified by recruitment centre.

This will be a three-phased comparison. Phase 1 (internal pilot) will confirm the expected rate of recruitment in 15 UK hospitals. Phase 2 (main phase) will extend the randomised comparison to a minimum of 40 UK hospitals. Phase 3 (long-term follow-up) will assess outcomes and costs for consenting participants via linkage to routine NHS datasets and by annual questionnaires.

8.1.1 Internal Pilot

The pilot will take place at 15 recruitment centres over a period of nine months. The aim of this initial phase will be to determine the number of eligible and recruited patients in the recruitment centres over the course of nine months.

Screening logs will be kept at each recruitment centre to determine the number of patients assessed for eligibility and reasons for any exclusion. The number of eligible and recruited patients, and the number of patients who decline consent or withdraw will be recorded. The Data and Safety Monitoring (DSMC) and Platform Oversight Committees (POC) will closely monitor recruitment during the feasibility phase and review the assumptions regarding the distribution of the primary outcome data in order to make a recommendation regarding continued progress of the comparison against the specified stop/go criteria (see section 11.7). If the comparison is stopped after the pilot phase, then all comparison participants will be followed up as per protocol. If the comparison continues into the main phase, participants from the internal pilot will be included in the final analysis.

8.1.2 Main phase

During the main comparison phase, patients will be recruited for a further 29 months from a minimum of 25 additional centres, bringing the minimum number of recruitment centres to 40 across the UK.

Participants will be allocated on a 1:1 basis to either fixation or hip replacement treatments. Both of these treatments are routinely used within the NHS. Clinical teams across the NHS are very familiar with both treatments.

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

Baseline demographic data will be collected as per the requirements in the master protocol (see section 12.2). When the patient is discharged from hospital, the local research team will check the participant medical records for any early complications.

At 6 weeks post-diagnosis, participants will be contacted by a member of the central trial office team to complete the EQ-5D-5L[8] and answer questions about their mobility using the mNMS, pain and residential status.

In addition to the data being collected at 4 months post-diagnosis of a hip fracture to satisfy the platform outcomes (see master protocol), a pain verbal rating scale (VRS) will be collected.

This same combination of questionnaires will be collected at 12-months post-diagnosis. Additionally, at 12 months a second review of medical notes will allow for the collection of further complications and contacts with the treating hospital. Routinely obtained radiographs relating to the hip fracture up until 12 months post-diagnosis will be collected.

8.1.3 Long-term follow-up

Linkages to routinely collected health care databases, national audits and registries of deaths will allow the collection of late adverse events and secondary care costs over a lifetime horizon and will initially be reported at five years following index treatment. Annual EQ-5D-5L and patient-reported complication data will be collected. This long-term follow-up will be reported separately to the main report.

9 COMPARISON PROCEDURES

A comparison flow chart is shown in Annex A.

9.1 PARTICIPANT IDENTIFICATION

9.1.1 Comparison participants

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

9.1.2 Inclusion criteria

- A minimally displaced intracapsular hip fracture that in the opinion of the treating surgeon may benefit from surgical treatment.

9.1.3 Exclusion criteria

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

- The fracture is only apparent on cross-sectional imaging.
- In the opinion of the treating surgeon the fracture cannot be fixed without a reduction manoeuvre.
- The fracture is complicated by local tumour deposits.
- There is clinically relevant pre-existing osteoarthrosis (OA) of the ipsilateral hip joint.

The incidence of severe OA in patients sustaining minimally displaced fractures is extremely rare (less than 5%).[13] Patients will be assessed by the treating surgeon to determine if there is clinically significant pre-existing functional pain that limits their mobility.

9.2 Consent

Patients will be presumed to have capacity unless established otherwise and the default will be to seek prospective individual consent from every patient. Where patients do not have capacity, those procedures laid down in Section 11.4 of the Master Protocol will apply.

With regards to these provisions, the randomised comparison described in this appendix is **not** a clinical trial of an investigational medicinal product.

9.3 Randomisation

Randomisation will be as per section 11.5 of the platform protocol. Randomisation will be on a 1:1 basis to arthroplasty or internal fixation, stratified by recruitment centre. The allocation sequence will be generated by the comparison statistician. Full details will be stored in a separate randomisation and blinding plan stored in the confidential statistics section of the trial master file.

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

9.4 Blinding

This will be a pragmatic randomised comparison so that the treating clinical team cannot be blinded to the treatment allocation. The outcome data will be collected from participants and entered onto the study central database by a research assistant in the study central office to reduce the risk of assessment bias. The participants in this comparison will not be informed which of the two treatments they have received. No formal assessment of the success or otherwise of the blinding will be made.

9.5 Description of the randomised treatments

9.5.1 Preoperative assessments

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. Supplementary imaging will be at the discretion of the treating clinical team. Routine investigations, anaesthetic assessment, antibiotic and venous thromboembolic prophylaxis will be used as per local policy.

9.5.2 Anaesthetic technique

A regional or general anaesthesia technique will be used for every participant as per routine clinical care. Intra-operative analgesia may be achieved by combining a local anaesthetic nerve block using either a nerve stimulator or ultrasound-guided technique, IV paracetamol 1g intravenous infusion and opiate analgesia as clinically indicated. Details of the anaesthetic technique will be recorded in the study CRF.

9.5.3 Surgical treatment

All participants will receive perioperative prophylactic antibiotics in accordance with current protocols agreed at each centre. Appropriate preparation, positioning and anaesthetic technique will be left to the discretion of the clinical team as per their normal clinical practice. Resources related to delivering treatment in both arms will be collected in study case report forms, including type of intervention received, admission and discharge date, complications and further treatments required. Participants will be randomly allocated to one of the treatment arms:

INTERNAL FIXATION

Internal fixation is usually performed using either a sliding hip screw or cannulated screws, with a recent trial showing no difference in outcome.[14] We will take a pragmatic approach, allowing surgeons to follow their usual practice for internal fixation.

Intraoperative fluoroscopy will be used to confirm that the fracture has not significantly displaced. The fracture will be fixed in-situ with no attempt to manipulate the fracture by closed or open means. Fixation will be achieved using a technique and implant chosen by the operating surgeon.

HIP REPLACEMENT

One of two types of hip replacement may be offered to people with hip fractures - hemiarthroplasty and total hip arthroplasty (THR). Patient position, surgical approach, implant and surgical technique will be chosen by the operating surgeon.

Details of the operation will be recorded in the study CRF.

9.5.4 Early post-operative care

All participants will be under the care of a multi-disciplinary team with input from a physician with an interest in hip fracture.

After surgery, key aspects of initial rehabilitation will be standardised; all participants will:

1. be encouraged to fully weight bear, and
2. attempt mobilisation on the day of, or first day after, surgery with a therapist.[7,15]

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.

The intensity and content of rehabilitation sessions provided within the acute hospital and in other inpatient settings or the community will be according to individual needs of the participant, within local resources. Details of this rehabilitation will be recorded in the study CRF.

9.6 Assessments

9.6.1 Schedule of assessments

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

Time Point	Data	Source	Setting
Baseline	i) Demographics ii) Relevant medical history iii) Injury details *Pre-injury:* iv) EQ-5D v) Residential status vi) Mobility status vii) Resource use	Participant or proxy & medical record	Acute inpatient - face to face; medical record review

Up to point of discharge	i) Treatment details including: a) Initial mobilisation details* b) Rehabilitation details* ii) Resource provision iii) Early complications	Medical records & therapist	Acute inpatient; Medical record review
6 weeks post-diagnosis*	i) EQ-5D ii) Pain VRS iii) Complications iv) Residential status v) Mobility status	Participant or proxy	Telephone, online or postal
4 months post-diagnosis	i) EQ-5D ii) Pain VRS* iii) Complications iv) Residential status v) Mobility status vi) Resource use	Participant or proxy & medical record	Telephone, online or postal
12 months post-diagnosis*	i) EQ-5D ii) Pain VRS iii) Complications iv) Residential status v) Mobility status vi) Resource use vii) Routinely collected radiographs	Participant or proxy & medical record and radiographs	Telephone, online or postal; medical record review
Yearly, up to 5 years post-diagnosis*	i) Mortality ii) Revision surgery iii) EQ-5D iv) Complications	i) & ii) Routinely collected hospital administrative databases (inpatient & emergency care); civil registers of deaths iii) Participant or proxy	i) & ii) NHS Digital, NHS Wales Informatics Service, Dept of Health (Northern Ireland) iii) Telephone, online or postal
Event driven – reporting of a related admission to hospital*	i) EQ-5D	Participant or proxy	Telephone, online or postal

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

*Key: *indicates measurement timepoint or data collected is in addition to the Platform Common Dataset specified in the master protocol*

9.6.2 Visits and Contacts

Contact 1: Details of the baseline contact are described in the Master Platform Protocol.

Contacts 2-8: Further follow-ups at 6 weeks, 4, 12, 24, 36, 48 and 60 months post-diagnosis, 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 choice expressed by the participant or proxy at the time of consent/declaration. All de-identified routinely acquired radiographs up until 12 months will be collected and transferred to the central study team.

Event-driven contact: Reporting of an expected and related, local SAE (a related local complication - as defined in Section 12.3.5 and 15.of the master protocol) by either the site staff, participant or proxy, will trigger collection of additional EQ-5D assessments. For participants yet to complete the first 4 months of data collection this will be a single additional EQ-5D report recorded by the site staff or participant/proxy as soon as possible after the event has been reported. For participants who have completed 4 months of data collection, this will be the index EQ-5D report (at the time of the event report) and two subsequent reports 4 and 8 weeks later.

9.7 Definition of End of Comparison

The end of comparison is the point at which the follow up of the last participant has been completed, all the data has been entered and all queries have been resolved. The last direct data collection will be at five years. The Sponsor and main Research Ethics Committee will be notified in writing within 15 days if the comparison has been concluded or terminated early.

10 SAFETY REPORTING

Safety reporting for each participant will begin from the time of consent and will end when the participant has reached their final follow up time point, at 5 years post-diagnosis. Investigators should follow up serious adverse events until resolved or the participant reaches 5 years post-diagnosis.

Due to the low risk of this randomised comparison and well-established safety profile of the interventions being investigated, adverse events that do not meet the definition of SAEs and unrelated SAEs are not required to be reported.

All unexpected serious adverse events (SAEs) are to be reported according to the guidelines specified in section 15 of the Master Protocol.

10.1 Related and expected Serious Adverse Events

These will be as per the master protocol.

11 STATISTICS & ANALYSES

11.1 Sample size determination

The sample size for this randomised comparison will be 878 participants.

Evidence on EQ-5D-3L utility values in similar patients is available from trials performed within the WHiTE cohort and WHITE trials.[16,17] These data suggest that the standard deviation for EQ5D-3L at 4 months post-diagnosis is approximately 0.3. The best evidence we have for an appropriate minimum clinically important

difference (MCID) is for EQ-5D-3; published estimates for MCID are in the range 0.05 to 0.085,[18] so an upper limit for the standardised effect size in hip fracture of approximately 2.8 or a 'small to moderate effect' based on Cohen's criteria.[19]

Assuming that the EQ-5D-5L at 4 months post-diagnosis has an approximate normal distribution, which is reasonable,[16,17,20] and a 1:1 allocation ratio, then if the true difference between the mean EQ-5D-5L in the two groups is 0.085, and the standard deviation is 0.3, we will need to recruit 263 participants in each group to be able to reject the null hypothesis that the population means are equal with 90% power and 5% (2-sided) significance. In a similar population from the WHiTE 3[17] and WHiTE 4[21] trials loss to follow-up was considerable, with 10% due to death prior to the four months timepoint, 20% for other types of loss to follow-up and 20% post-randomisation withdrawals (due to participants declining consent on the recovery of capacity – see paragraph 9.2). As deaths can be incorporated into the utility scores, with a score of 0, we would assume that 60% of recruited comparison participants will provide the primary outcome. In summary, 526 participants with primary outcome data are required to allow us to detect a difference of 0.085 assuming a standard deviation of 0.3 with 90% power and a 5% 2-sided significance. To ensure this while allowing for 40% loss to follow-up gives an anticipated target of 878 randomised participants (439 per arm).[17,21]

11.2 Analysis populations

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

The ITT population includes all randomised participants including:

1. Participants who are randomised but do not undergo surgery (such as those who died or were found to be ineligible after randomisation but before surgery).
2. Participants who are randomised and die after surgery with a consultee declaration signed but before post-diagnosis consent has been confirmed.
3. Participants who are randomised and found to be ineligible during or after surgery.

Note: participants who withdraw from the comparison between randomisation and 5 years will provide data up to the point of withdrawal.

The per protocol population will be the ITT population excluding participants as described in 1 and 3 above and other major deviations from the protocol which will be fully described in the Statistical Analysis Plan.

11.3 The level 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). All p-values will be reported to 3 decimal places. 95% confidence intervals will be reported throughout.

11.4 Statistical Analysis

A fully detailed comparison SAP will be prepared for FRUITI, including the additional outcomes and timepoints to those described in the Master Platform SAP. The Master and comparison SAPs will be finalised after review by the DSMC and POC prior to any final analysis data-lock. Any subsequent changes to the master or comparison SAPs will be justified in the final report. The analyses for this comparison are summarised here**.**

Analyses will be performed using the intention-to-treat principle including all randomised participants according to allocated treatment with additional per protocol analyses will be undertaken as sensitivity analyses. Results will be reported as per the CONSORT Statement. Secondary endpoints will be presented without formal multiplicity adjustment.

The primary outcome, EQ-5D-5L index score, will be analysed using a mixed-effects model over all available timepoints (baseline; 6 weeks; 4 months; 12 months) with 4 months as the primary endpoint. The model will be adjusted for important prognostic factors (sex, age) as fixed effects, and include centre as a random effect as per the Platform Master Protocol section 16. The treatment effects will be presented as an adjusted mean difference with a 95% confidence interval and corresponding 5% (2-sided) p-value.

The secondary outcome of pain VRS will be analysed using an ordinal mixed-effects regression model over all timepoints, adjusted for the same factors as the primary outcome. Summaries of complications and safety events will be presented, and total numbers of participants experiencing at least one complication or adverse event will also be compared between treatment arms using a logistic mixed-effects regression model.

During the recruitment period, the data collection tool used for the assessment of mobility (secondary outcome) was changed from the *NHFD mobility questions* to the *modified New Mobility Score*. Data collected through the two outcome tools will be summarised separately at the end of the study, with the anticipation that sufficient data will be collected with the new data collection tool to provide a meaningful comparison between treatment groups and to address the relevant objective

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11.5 Health economic analysis

A fully detailed economic evaluation analysis plan (HEAP) will be drafted early in the comparison and finalised after review by the DSMC and TSC. The economic evaluation will determine cost-effectiveness in relation to quality-adjusted life years (QALYs) from an NHS and personal social services perspective at 12 months post intervention. 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 report separately private expenses, informal care, and productivity losses incurred in both arms.

Any missing QALYs and costs will be jointly imputed using multiple imputation chained equations. Cost and QALY estimates will be bootstrapped and adjusted for comparison stratification variables (centre) and other potential variables as per the statistical analysis plan, such as age, gender and cognitive impairment, in secondary analyses. “All available” and “imputed” cost categories and QALY data, will be reported by comparison arm in a cost-consequences framework. The cost-effectiveness parameter will be the bootstrapped incremental net monetary benefit statistic (INMB) derived using the 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. In a cost-effectiveness acceptability curve, we will depict the probability of the interventions being cost-effective at a range of willingness to pay thresholds to illustrate the uncertainty around the adoption decision. In one-way and sensitivity analyses we will vary methodological assumptions to gauge robustness of results.

In a secondary analysis, for comparable results with the planned 5 years economic evaluation, we will re-estimate the cost-effectiveness parameter at 12 months using secondary care inpatient and emergency department cost data only.

11.6 Long-term analyses

The first long-term analysis will be reported when each living participant has reached five years of follow-up.

Hospital 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. For each treatment group, statistical models will be estimated to investigate the association between treatment and death and re-operations. Operations for infections and dislocations will be identified by a combination of corresponding International Classification of Diseases (ICD; diagnostic) and Office of Population Censuses and Surveys (OPCS; procedure) codes, whilst all-cause reoperations will be identified by OPCS codes only. Similar work has been undertaken before by Pinedo–Villanueva as well as other researchers, with relevant codes readily available.[22–24] Reoperations will include joint manipulations under anaesthesia or open reductions, debridements for infection, fixation for periprosthetic fracture and revisions for dislocation, infection or fracture (all in hip replacement arm); debridements for infection, revision fixation and revision to hip replacement (all in fixation arm). As dislocations are limited to those with a hip replacement, we will compare the rate of dislocation between those originally undergoing primary hip replacement and those receiving replacement after a failed fixation.

For consistency between the short and long-term economic analyses (the latter based on routinely collected data), we will compare the number of fracture-related inpatient stays and emergency department (ED) visits reported in the RCD datasets at 1 year, with the short-term, 12 months participant data on hospitalisations and ED attendances for each treatment group. This will help provide context for interpretation of the long-term follow-up.

11.7 Decision points

A total of 878 participants will be randomised across a minimum of 40 recruitment centres. We will exploit the efficiencies available from nesting this within the Platform. This Platform has been built based upon the experiences of the White Cohort Study which has successfully delivered three hip fracture trials[16,17,25] and three further trials are currently underway (ISRCTN92825709, 18393176, 15606075). The comparison processes are streamlined and harmonised with those of the Platform so that we should be able to achieve 65% recruitment of eligible patients and 90% follow-up of available participants (those alive and not withdrawn) at the primary outcome time-point.

During the 9 months internal pilot phase, we expect to recruit 80 patients from the 15 pilot recruitment centres. The DSMC and POC will closely monitor recruitment during the feasibility phase and make a recommendation to the funder regarding continued progress of the comparison against the specified stop/go criteria. If recruitment is below 60 participants, we will consider stopping the comparison for feasibility reasons; if between 60 and 80 participants we will review the recruitment processes and implement the committees' recommendations. In the event that recruitment is lower than anticipated we have a network of 120 hospitals in addition to these 40 that have previously worked with us on multicentre trials.

If the comparison is stopped, then all comparison participants will be followed up as per protocol. If the comparison continues into the main phase, participants from the internal pilot will be included in the final analysis.

Following the pilot phase, a minimum of a further 25 recruitment centres will be involved with recruitment, which will be completed within a total of 29 months. Those patients recruited during the pilot phase will be included in the final sample.

12 DISSEMINATION POLICY

The main outputs for FRUITI will be released within 12 months of the end of the main follow-up data collection time-point at 1-year post-diagnosis of a hip fracture. Outputs for the long-term analysis will be released within 12 months of the end of the final data collection time-point at 5 years post-diagnosis.

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

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

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14 ANNEX A: FLOW CHART