

# The World Hip Trauma Evaluation Study 3

HEMIARTHROPLASTY EVALUATION BY MULTICENTRE INVESTIGATION –  
WHITE 3: HEMI – AN ABRIDGED PROTOCOL



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## Background

Approximately half of all hip fractures are displaced intracapsular fractures. The standard treatment for these fractures is either hemiarthroplasty or total hip arthroplasty. The recent National Institute for Health and Care Excellence (NICE) guidance on hip fracture management recommends the use of ‘proven’ cemented stem arthroplasty with an Orthopaedic Device Evaluation Panel (ODEP) rating of at least 3B (97% survival at three years). The Thompsons prosthesis is currently lacking an ODEP rating despite over 50 years of clinical use, likely due to the paucity of implant survival data. Nationally, adherence to these guidelines is varied as there is debate as to which prosthesis optimises patient outcomes.

## Design

This study design is a multi-centre, multi-surgeon, parallel, two arm, standard-of-care pragmatic randomised controlled trial. It will be embedded within the WHITE Comprehensive Cohort Study (ISRCTN63982700). The main analysis is a two-way equivalence comparison between Hemi-Thompson and Hemi-Exeter polished taper with Unitrax head. Secondary outcomes will include radiological leg length discrepancy measured as per Bidwai and Willett, mortality, re-operation rate and indication for re-operation, length of index hospital stay and revision at four months. This study will be supplemented by the NHFD (National Hip Fracture Database) dataset.

## Discussion

Evidence on the optimum choice of prosthesis for hemiarthroplasty of the hip is lacking. National guidance is currently based on expert opinion rather than empirical evidence. The incidence of hip fracture is likely to continue to increase and providing high quality evidence on the optimum

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## Article focus

- Provision of an abridged protocol for the WHITE 3: HEMI study.
- Allow transparency of study methods and design.

## Key messages

- Outcomes to be published late 2016.

## Strengths and limitations

- Rigorous design.
- Optimal primary outcome measure for this patient cohort (EQ-5D).

## Introduction

Proximal femoral (hip) fractures are one of the greatest challenges facing the medical community. In 1990, a global incidence of 1.31 million was reported and was associated with 740 000 deaths.<sup>1</sup> Hip fractures constitute a heavy socioeconomic burden worldwide. The cost of this clinical problem is estimated at 1.75 million disability adjusted life years lost, 1.4% of the total healthcare burden in established market economies.<sup>1</sup>

## Existing knowledge

Hip fractures can be subdivided into intra and extracapsular fractures. Approximately half of all hip fractures are intracapsular, and the majority of these are displaced (Type AO/OTA B3).<sup>2,3</sup> The accepted treatment for a displaced intracapsular fracture is an arthroplasty. This includes hemiarthroplasty (HA), where the proximal femur is replaced, and total hip arthroplasty (THA), where both the femur and acetabulum are replaced.

The Thompson's prosthesis is a press fit hemiarthroplasty implant designed in the pre-cement era. It is now most frequently cemented, with improved clinical effectiveness compared with uncemented monoblock (Austin-Moore) stems.<sup>4</sup> Its offset is fixed as it rests just above the lesser trochanter. In addition, the placement of the neck cut can be varied. The prevalence of leg length discrepancy following the use of a Thompson prosthesis is unknown. The Orthopaedic Device Evaluation Panel (ODEP) produces ratings for hip arthroplasty prostheses used in the United Kingdom, based on length of follow-up and quality of evidence. The Thompson's stem currently does not have an ODEP rating, due to the relative paucity of implant survival data in this at-risk patient group.

The National Institute for Health and Care Excellence (NICE) offers evidence-based guidance to clinicians in the United Kingdom. The recent NICE guidance on hip fracture management recommends the use of 'proven' cemented stem designs with an ODEP rating of at least 3B (97% survival at three years), instead of the Thompson's prosthesis.<sup>5</sup> Recent evidence published since the NICE guidance however supports the use of the Thompson stem.

The Thompsons stem has been used extensively in the United Kingdom for over 50 years. Until recently, there has been a lack of evidence of implant survival but the implant is in common use in all the investigating units of this study and large series have recently been published demonstrating a low complication rate and excellent implant survival. One study of 430 patients followed to at least five years showed a dislocation rate of 1.4% and a revision rate of 1.2%.<sup>6</sup> Another recent series of 1670 patients followed to five years reported implant survival at 95.4% - equivalent to a higher ODEP 5 status.<sup>7</sup>

There are conflicting global trends for the use of Thompson's prosthesis in favour of newer stems. A well-constructed but underpowered study showed no difference in hip function, pain, complications or mortality at 12 months.<sup>8</sup> A recent review of the Swedish Hip Arthroplasty Register has reported a decline in the proportion of Thompson's stems from 9% to 1% from 2005 to 2009 with an increasing number of unipolar modular prostheses being implanted.<sup>9</sup> The 2011 annual report from the Australian National Joint Registry found that the use of the Thompson's prosthesis had increased in 2010 (30.6% of all monoblocks, up from 20.9% in 2003), however the

number of monoblock stems was declining compared with monoblock modular and bipolar implants.<sup>10</sup>

The Exeter stem is a well proven design and is consistent with current NICE guidance. It allows for leg length adjustment and offset. One recent non-randomised study found that an unacceptable leg length discrepancy was 1.4 times more likely to occur with the Thompsons stem compared with the Exeter Trauma Stem,<sup>11</sup> which is of a similar shape. Leg length discrepancy has been shown in recent studies of hip replacement to influence both hip function (WOMAC) and health status (EQ-5D).<sup>12,13</sup> The Exeter stem is also in common use in the investigating units of the current study.

**Aim of the trial.** The aim of this trial is to compare the health-related quality of life (HRQoL) of patients receiving a cemented Thompsons *versus* an Exeter cemented polished taper stem for displaced intracapsular fractures of the proximal femur requiring hemiarthroplasty.

**Good clinical practice.** The trial will be carried out in accordance with good clinical practice (GCP) and in accordance with the following protocol.

**CONSORT recommendations.** The trial will be reported in line with the CONSORT statement.<sup>14</sup>

## Trial design

**Design summary.** This study will be a multi-centre, multi-surgeon, two-arm parallel group, randomised standard-of-care controlled trial. It will be embedded within the WHiTE Comprehensive Cohort Study (ISRCTN 63982700). The WHiTE Study is a large cohort study examining a range of outcomes including the EQ-5D (validated health status measure).<sup>15</sup> in patients following hip fracture. The WHiTE study allows embedding of randomised controlled trials within this patient cohort.<sup>16</sup> The trial will include a two-way equivalence comparison between Hemi-Thompson and Hemi-Exeter polished taper with Unitrax head (Stryker, Kalamazoo, Michigan). The trial is planned to last a total of 28 months.

It is expected that participant recruitment will take 18 months and final follow-up will be at four months. Based upon 2013 data in the National Hip Fracture Database (NHFD) the involved units perform approximately 890 of such procedures per year.

Trial management will be conducted at Warwick Clinical Trials Unit in accordance with standard operating procedures.

**Hypothesis.** The null hypothesis is that there is no difference in HRQoL at four months post injury between patients over 60 years of age with an AO/OTA type B3 fracture of the proximal femur treated with an Exeter polished taper/Unitrax *versus* a Thompson hemiarthroplasty.

**Objectives.** The primary objective is:

- To quantify and draw inferences on observed differences in patients' HRQoL between the trial treatment groups at four months post-injury.

The secondary objectives are:

- To quantify and draw inferences on observed differences in the functional outcomes between the trial treatment groups.
- To quantify and draw inferences on observed differences in the proportion of all cause repeat surgery between the trial treatment groups.
- To quantify and draw inferences on observed differences in the proportion of complications between the trial treatment groups.

**Outcome assessment.** We will augment the existing NHFD dataset with radiographic fracture pattern and EQ-5D-5L<sup>15</sup> at baseline (retrospective pre-fracture) and 120 days post-fracture. 120 days represents a routine follow-up point for the NHFD, and the point at which recovery following hip fracture plateaus. Parsons et al<sup>17</sup> reported that EQ-5D improved after surgery to around four months, with little evidence for subsequent improvement after this time-point.

In addition, copies of the participants' routine "operation note" and "discharge summary" will be collected. The discharge summary includes details of their treatment, peri-operative complications and discharge address.

**Primary outcome measure.** The primary objective of this trial is to quantify and draw inferences on patient's HRQoL between treatments based on observed differences as shown by a validated, patient-reported, quality of life questionnaire collected at four months post-injury – EQ-5D-5L. Proxy reporting of EQ-5D will be used in the event of participants lacking capacity to consent. Parsons et al<sup>17</sup> demonstrated that an EQ-5D reported by proxies (relatives and carers) behaves similarly to self-reported scores.

The use of the EQ-5D as a primary outcome measure is based upon work that found that the EQ-5D increased until four months, at which point the EQ-5D plateaus. Between four and 12 months post-operative improvement in the EQ-5D score was minimal. When this is balanced against the gradually increasing mortality rates in this patient cohort, a follow-up time of four months has been decided upon, which will represent a point of maximum benefit from hip fracture surgery, whilst minimising loss to follow-up through mortality.

**Secondary outcome measure.** The secondary objectives of the study are to quantify and draw inferences on the efficacy of the group based on observed differences as shown by:

- Radiological leg length discrepancy measured as per Bidwai and Willett;<sup>11</sup>
- Mortality;
- Re-operation and cause;
- Length of index hospital stay;
- Revision at four months.

Participant outcomes will be collected at baseline (pre-injury status recorded upon admission to hospital) and 120 days post-surgery as per the current requirement for the NHFD. This will include data on delays to surgery and the surgeon's seniority

**Health economic measures.** The patient-recorded outcome data will be combined with mortality data extracted from the NHFD to estimate a quality-adjusted life year (QALY) profile for each patient. This will allow us to estimate the production of health associated with the surgical procedures and treatment pathways for each participant.

**Eligibility.** Patients will be screened in the daily trauma meetings at each recruiting hospital.

#### **Inclusion criteria**

- All patients presenting to the collaborative with an AO/OTA type B3 fracture of the hip.
- Patients who the treating Consultant Orthopaedic Surgeon believe will benefit from hemiarthroplasty.

#### **Exclusion criteria**

- Patients younger than 60 years of age;
- Patients with pre-existing symptomatic hip arthritis;
- Patients who are managed non-operatively.

**Post-recruitment withdrawals and exclusions.** Participants may withdraw from the study at any time without prejudice. The participants may be withdrawn from the study at the discretion of the Chief Investigator due to safety concerns. Throughout the study, screening logs will be kept to determine the number of patients assessed for eligibility and reasons for any exclusion. Patients who decline to continue to take part will be given the opportunity to discuss/inform the research team of the reasoning behind their decision not to take part.

**Consent.** Patients with a hip fracture are a clinical priority for urgent operative care. They will undergo surgery on the next available trauma operating list. All patients with a fracture of the hip are in pain and have received opiate analgesia. It is therefore understandable that patients find the initial period of their treatment in hospital confusing and disorientating. Similarly, patients' next of kin, carers and friends are 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 surgery (where possible) and informing the patient and any next of kin about immediate clinical care. It is often not possible for the patient/consultee to review trial documentation, weigh the information and communicate an informed decision about whether they would wish to participate.

Conducting research in this 'emergency setting' is regulated by the Mental Capacity Act 2005.<sup>18</sup> As patients are likely to lack capacity as described above, and because of

the urgent nature of the treatment limiting access to, and appropriate discussion with Personal Consultees, we will act in accordance with section 32, subsection 9b of the Mental Capacity Act following a process approved by the relevant research ethics committee. Those patients who have surgery on the next available trauma operating theatre will enter the study under presumed consent; we will not obtain consent prior to surgery, but will approach an appropriate consultee. Where a Personal Consultee is available, they will be provided with the study information. The Personal Consultee will be given the opportunity to ask questions and discuss the study, after which their oral agreement will be recorded. Where a Personal Consultee is not available, a Nominated Consultee will be identified to advise the research team. The Nominated Consultee will be the patient's treating Trauma and Orthopaedic Surgeon. If that surgeon is a member of the research team, another independent surgeon will be identified.

At the first appropriate time when the patient has regained capacity (this will usually be on the first day after surgery) the research associate will provide the patient with the study information. The patient will be given the opportunity to ask questions and discuss the study with their family and carers for as long as they require. They will then be asked to provide written consent for continuation in the study. If the patient does not wish to complete questionnaires for the study at this stage, they will be asked if they are happy to provide written consent for the research team to access and use any routinely collected NHS data, including those collected through the NHFD. Alternatively the patient can choose to decline participation completely. The original signed consent form will be kept in the investigator site file. Three copies of the consent forms will be made; one held in the patient's medical notes, one for the patient and one copy for the study team.

On occasion, patients may be able to provide consent before their operation; for example those whose surgery has been delayed for clinical reasons. These patients will be approached by the research team before their operation for consent to participate in the study. Some patients, whose surgery has been delayed, may still not have capacity, e.g., those who are acutely confused. In this case, the research team will approach a consultee for agreement that the patient participate in the study. The patient themselves will be approached for consent as soon as the clinical team deems that the patient has regained capacity following their operation.

Best efforts will be made to involve participants who, temporarily or permanently, lack the capacity in the decision to be involved in the study. 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. Appropriate information will be communicated to the participant and updated as their understanding changes. At all times, the study

team will act in accordance with the participants' best interests.

Any new information that arises during the study that may affect participants' willingness to take part will be reviewed by the Trial Steering Committee; if necessary this will be communicated to all participants and a revised consent form completed.

Responsibility for recording and dating both oral and written informed consent or agreement will be with the investigator, or persons designated by the investigator, who conducted the informed consent discussion. Designated responsibility should be recorded on the site delegation log.

**Recruitment.** Participant recruitment began in February 2015.

Pre-enrolment eligibility checks will be carried out by the study team to ensure that participants are not enrolled in error. Participant consent, personal or nominated consultee agreement will be documented. Inclusion of the participant in the study will be recorded in the clinical notes by the research associate.

If the participant withdraws from the study completely, data collected up until the point of withdrawal will be included in the final analysis. Those participants who die before consent/agreement can be obtained will not be included in the study to avoid distressing the relatives unnecessarily. For those participants who die before consent/agreement can be obtained, routinely collected hospital data that are useful and relevant to the trial will be recorded up until the patient's death. This will be included in the final analysis. We will not complete participant questionnaires or include the participants in the trial beyond this to avoid distressing the relatives unnecessarily.

**Power and total sample size.** Sample size is calculated based on a superiority design. The best available evidence we have from data collected during the WHIT and WHITE studies suggests that the standard deviation for EQ-5D at four months post-surgery is approximately 0.3 points.<sup>17</sup> The best evidence we have for what an appropriate minimum clinically important difference (MCID) is for EQ-5D comes from the paper by Walters and Brazier.<sup>19</sup> After a review of the appropriate literature, the authors estimated a median value of 0.08 for the MCID for EQ-5D. Using our best estimate of the standard deviation ( $SD = 0.3$ ), this suggests a standardised effect size of approximately 0.24. This is reassuring, as it is exactly equivalent to the mean MCID that Walters and Brazier report in their literature review, and is what we might classify as a 'small to moderate effect' based on Cohen's criteria.<sup>20</sup> Taking a conservative approach, we design the study using a marginally smaller MCID. Therefore, we consider values ranging from 0.07 to 0.08 (Table I).<sup>21</sup>

Assuming that the EQ-5D at four months post-surgery has an approximate normal distribution, which Parsons et al<sup>17</sup> suggests is reasonable, and using a 1:1 allocation



**Table 1.** Minimum clinically important difference (MCID) for EQ-5D<sup>21</sup>.

Power	MCID		
	0.07	0.075	0.08
80%	290	252	222
90%	387	337	297

ratio, then if the true difference between the experimental and control group EQ-5D means is in the range from 0.07 to 0.08, we will need to recruit the below number of participants in each group to be able to reject the null hypothesis that the population means are equal with probability (power) 0.8 and 0.9 and type I error rate of 5% (significance).

Taking the intermediate MCID of 0.075, suggests for 80% power, we would need to recruit 252 patients in the experimental arm and 252 in the control arm (544 in total). In this population we expect some considerable loss to follow-up due mainly to patient death, so we will assume that only 70% of recruited study participants will be available at the definitive end point at four months. This gives a total sample size of 720 for 80% power and 964 for 90% power. The latter is recommended for scientific rigor. So our best estimate of the minimum sample size required to detect a difference between these groups is 964.

**Treatment allocation.** Participants will be randomised to one of two groups:

Group one: Thompsons hemiarthroplasty;

Group two: Polished taper Exeter and Unitrax head.

Allocation sequences will be created using a computer-generated random number sequence. Patients will be allocated using secure, online randomisation via a distant computer generated system administered by Warwick Clinical Trials Unit (CTU). In the event of technical difficulties, a dedicated randomisation phone line will be available from Warwick CTU. Participants will be enrolled by the operating surgeon or trial research associates. Participants will be assigned to their treatment allocation prior to the time of surgery by accessing the online randomisation programme. This will allow for treatment allocation to be implemented outside of working hours.

The treatment allocation will be stratified by trial centre, age (< 80 and 80 + years) and gender, using a minimisation procedure implemented by Warwick CTU. The surgery will be performed under the care of any of the consultant surgeons in the collaborating centres. The large number of surgeons and the wide skill mix should eliminate the 'surgeon effect' such that stratification by surgeon is not required.<sup>22</sup>

**Blinding.** Participants will be blinded to the treatment allocation. The operating surgeon cannot be blinded to the allocation but will take no part in the assessment of the primary outcome measurement, which will be determined from patient interview and the clinical record. The EQ-5D is a

patient reported measure. Patients will be kept blinded until the completion of the trial when the blind is broken. There will be no formal analysis of the success of the blinding.

Leg length inequality will be performed independently, and will be unblinded.

**Trial treatments: pre-operative assessment.** Participants will usually be assessed in the Emergency Department. Diagnosis of a hip fracture will be confirmed by a plain AP radiograph of the pelvis, and further imaging as required.

Participants will be transferred to an Orthopaedic Trauma ward and will receive pragmatic standard care, as per the NICE guidelines.<sup>5</sup>

**Trial treatments: anaesthetic technique.** A regional or general anaesthesia technique will be used for every participant.

**Surgical intervention.** The approach and operative technique employed will be at the discretion of the operating surgeon.

**Post-operative rehabilitation.** Post-operative analgesia will be prescribed intra-operatively and reviewed by the responsible clinical teams as appropriate.

Centres will aim to provide all participants with a clinical review by a Specialist Orthogeriatrician within 72 hours of admission. This will include a fracture prevention assessment. Assessment and treatment of participants' for osteoporosis will be carried out in accordance with current NICE guidance.<sup>23</sup> Similarly, participants' risk of falling will be assessed in accordance with BOA guidance.<sup>24</sup>

Participants will be discharged from the acute Orthopaedic Trauma Ward at the earliest safe opportunity as per routine practice and to the most appropriate discharge destination as determined by the multi-disciplinary team.

**Study assessments.** Table II describes the assessments and interventions that will be carried out during the period that each participant is involved in the study.

**Methods and assessments.** Participants will be followed up centrally unless a site opts to collect the information locally.

We will use techniques to ensure minimum loss to follow-up - multiple contact addresses, telephone numbers, mobile numbers and email addresses will be collected during enrolment.

We will attempt to contact the participant or next of kin on several occasions via telephone. If this fails, we will send the participant or next of kin a postal questionnaire to complete with a pre-paid return envelope. Finally, the General Practitioner of those participants who are deemed 'lost-to-follow-up' will be contacted in order to attempt to complete it. If all these methods fail, we will class the participant as a non-responder for that time point.

**Quality of Life (EQ-5D).** EuroQoL (EQ-5D-5L)<sup>15</sup> to be collected pre operatively and four months post-operatively. The EQ-5D 5L is a validated self-administered patient-reported outcome measure widely used and requires less than ten minutes to complete. This is a generic HRQoL

**Table II.** Study assessments.

	Study assessment points	Baseline	4 Months
Core dataset	Inclusion/exclusion	Yes	
	Contact details	Yes	
	Past medical history	Yes	
	EQ-5D	Yes	Yes
	Leg length		Yes
	Operation note	Yes	
	Discharge summary	Yes	
	Complications	Yes	Yes
NHFD	Present condition	Yes	
	Functional status pre-admission	Yes	
	Functional status	Yes	Yes
	Hospital information – admission	Yes	
	Hospital information – surgery	Yes	
	Hospital information – treatment	Yes	
	Hospital information – discharge	Yes	

measure consisting of five dimensions, each with a five-level answer possibility. Each combination of answers can be converted into a health utility score. It has good test-retest reliability, is simple for patients to use, and gives a single preference-based index value for health status that can be used for broader cost-effectiveness comparative purpose. EQ-5D scores can also reasonably be collected from proxies (relatives and carers).

**Radiological leg length.** Leg length will be assessed by drawing a true horizontal transverse line between the centre of the contralateral femoral head and the centre of the prosthetic femoral head. A second line in the axis of the femoral shaft is drawn through the greater trochanter, bisecting to the horizontal line. The vertical distance from the tip of the greater trochanter to horizontal is to be taken as the neck length. A range of 5 mm proximal or distal as compared with the contralateral side is considered acceptable. The outcome measure will be satisfactory or unsatisfactory leg length.<sup>11</sup>

**Functional status.** Functional status will be assessed in line with the NHFD routine dataset. This will include one question related to walking ability indoors and outdoors and information of any bone protection medication taken.

**Complications.** Adverse events will be recorded into a complications reporting form at each site and sent to the central office monthly. These will be recorded and reported annually to the sponsor and ethics committee.

### Data management

**Data collection and management.** Personal data collected during the trial will be handled and stored in accordance with the 1998 Data Protection Act and Warwick CTU Standard Operating Procedures.

It is likely that some data may not be available due to voluntary withdrawal of participants, lack of completion of individual data items or general loss to follow-up. Where possible the reasons for missing data will be ascertained and reported.

**Case report forms.** The case report forms (CRFs) will be designed by the Trial-Coordinator in conjunction with

the Chief Investigator, Co-Investigators and Statisticians. Hospital sites will send original copies to Warwick CTU in a pre-paid envelope. Alternatively, forms can be sent electronically, using a secure NHS.net email account. Data will be entered onto a database by a member of the trial team, and will be subject to validity checks and additional data-checking procedures in order to assure quality of data entry. The original CRF will be securely stored in archiving approved and overseen by the Unit Quality Assurance Manager. The additional copies will be kept and stored at each hospital site in the Investigator Site File and kept for a minimum of ten years, or as required by Trust regulations at each particular hospital site, whichever is longer.

Patient contact details and consent forms will be removed from the CRF booklet and the original top copy returned to the WHiTE 3: HEMI trial office separately to the CRF booklet to maintain participant anonymity, and only if consent has been given.

**Database and management.** The data collected from participants listed in Table I will be entered in the trial database. The study databases will be set up by a Warwick CTU computer programmer according to standard operating procedures and all specifications agreed between the Computer Programmer, Statistician and Trial Co-ordinator. The procedure for data entry will be documented in the data management plan. In the case of any interim analysis, the database will be frozen at the analysis time point. Data collected after this point will not be included in the interim report. We will send data collected at follow-up to the NHFD via a secure NHS.net email account for them to input using the participant DOB and NHS number as identifiers. NHS.net is a secure, encrypted way of transferring data recommended for use between NHS Trusts.

**Data access and quality assurance.** All data collected will be anonymised after the collection of the baseline demographic data, and all participants given a unique study number at the point of randomisation. Identifiable participant data will be held on a separate database and in a locked filing cabinet and coded with a study participant number to tag identifiable data to the outcome data. Names and addresses will not be disclosed to anyone other than staff involved in running the study.

Disclosure of confidential information will only be given if a participant indicates an issue which may jeopardise the safety of the participant or another person.

Direct access to source data/documentation may be required for study-related monitoring or audit by Warwick CTU, regulatory authorities, NHS Trust R&D staff, or ethic committees.

**Data storage.** All paper data will be stored in a designated storage facility in the Clinical Trials Unit at Warwick. Electronic data will be stored on password protected university computers in a restricted access building. Access will be restricted to authorised personnel.

**Archiving of trial data.** Data will be archived in accordance with Warwick CTU guidance.

## Data analysis

**Data validation.** Prior to formal analysis, data will be checked for outliers, missing values and validated using the defined score ranges for all outcome measures. Queries will be reported to the Trial Co-ordinator and investigated. Standard statistical summaries (e.g., medians and ranges or means and variances, dependent on the distribution of the outcome) and graphical plots showing correlations will be presented for the primary outcome measure and all secondary outcome measures. Baseline data will be summarised to check comparability between treatment arms, and to highlight any characteristic differences between those individuals in the study, those ineligible, and those eligible but withholding consent.

**Missing data.** It seems likely that some data may not be available due to voluntary withdrawal of patients, lack of completion of individual data items or general loss to follow-up. Where possible the reasons for data ‘missingness’ will be ascertained and reported. Although missing data are not expected to be a problem for this study, the nature and pattern of the missingness will be carefully considered — including in particular whether data can be treated as missing at random (MAR). If judged appropriate, missing data will be imputed. Any imputation methods used for scores and other derived variables will be carefully considered and justified. If the degree of missingness is relatively low, as expected, the primary analysis will be based on complete cases only (complete case analysis), with analysis of imputed datasets used to assess the sensitivity of the analysis to the missing data. Reasons for ineligibility, non-compliance, withdrawal or other protocol violations will be stated, and any patterns summarised. More formal analysis, for example using logistic regression with ‘protocol violation’ as a response, may also be appropriate and aid interpretation.

## Analysis of clinical effectiveness

**Primary outcome.** The main analysis will investigate differences in the primary outcome measure, EQ-5D (HRQoL), between the two treatment groups on an intention-to-treat basis at four months from the index fracture. The differences between treatment groups will be assessed using a Student *t*-test, based on a Normal approximation for EQ-5D. Tests will be two sided and considered to provide evidence for a significant difference if *p*-values are less than 0.05 (5% significance level). Estimates of treatment effects will be presented with 95% confidence intervals.

The minimisation procedure used for randomisation will ensure balance in treatment allocation across recruiting centres, age groups (< 80 and 80 + years) and gender. However, in addition to the unadjusted analyses (*t*-tests) we will also undertake regression analyses to adjust for any imbalance between treatment groups in patient baseline (pre-injury) EQ-5D, age and gender. The fixed effects analysis (linear regression model) will also be generalised

by adding a random effect for recruiting centre to allow for possible heterogeneity in patient outcomes due more generally to the recruiting centre. The mixed-effects regression will be the definitive analyses and will be undertaken using the specialist mixed-effects modelling functions available in the software package R (R Foundation, Vienna, Austria). EQ-5D data will be assumed to be approximately normally distributed; possibly after appropriate variance-stabilising transformation. The primary focus will be the comparison of the two treatment groups of patients, and this will be reflected in the analysis which will be reported together with appropriate diagnostic plots that check the underlying model assumptions. Results will be presented as mean differences between the trial groups, with 95% confidence intervals.

**Secondary outcomes and complications.** Secondary analyses will be undertaken using the above strategy for approximately normally distributed outcome measures; length of index hospital stay (after log-transform). For dichotomous outcome variables, such as leg length discrepancy, indicators of revision and other complications related to the trial interventions, mixed effects logistic regression analysis will be undertaken with results presented as odds ratios (and 95% confidence intervals) between the trial groups. The temporal patterns of any complications will be presented graphically and, if appropriate, a time-to-event analysis (Kaplan-Meier survival analysis) will be used to assess the overall risk and risk within individual classes of complications (e.g., revision) and death. Cox’s proportional hazards regression will be used to test for differences in death rates between the trial intervention groups, after adjusting for age and gender. Multiple complications will be defined as two or more independent events, i.e., not continuations of a previous complication, for the same patient and will be identified only after discussion with the clinical team.

**Plan of analysis.** The statistical analysis plan (SAP) will be agreed with the Data management Committee (DMC) at the start of the study. Any subsequent amendments to this initial SAP will be clearly stated and justified. Interim analyses will be performed only where directed by the DMC. All statistical analyses will be carried out using software package R.

## Trial organisation and oversight

**Trial Oversight Committee.** A Trial Oversight Committee will be convened and independently chaired in accordance with the University of Warwick CTU standard operating procedures. All issues pertaining to the management of the trial will be co-ordinated by the Trial Steering Committee. The schedule for meetings of the committee will be as follows:

- Meeting one: trial commencement;
- Meeting two: interim meeting at 50% recruitment;
- Subsequent meetings: end of trial.

**Data monitoring committee.** A data monitoring committee will be convened and review data once the trial has recruited 50% of the target.

**Trial management group.** A trial management group will meet on a monthly basis in order to explore issues pertaining to the day-to-day running of the trial.

**Trial registration.** The trial has been registered with the International Standard Randomised Controlled Trial Number Register. ISRCTN 39085558.

**Unblinding.** Unblinding will occur for clinical management purposes only. In exceptional circumstances beyond this, agreement will be sought from the Chief Investigator and statistician before the blind is broken.

**Interim analysis.** Interim analysis will only be conducted upon the Data Monitoring Committee's request.

**Indemnity/compensation/insurance.** All issues of indemnity, compensation and insurance are detailed in the sponsorship statement of Northumbria Healthcare NHS Foundation Trust.

**Monitoring and quality assurance policy.** Quality control procedures will be undertaken during the recruitment and data collection phases of the study to ensure research is conducted, generated, recorded and reported in compliance with the protocol, GCP and ethics committee. The Chief Investigator and trial coordinator will conduct sampling of the database as per the data management plan in order to identify any problems in trial procedures.

**Dissemination and publication.** The results of this trial will be disseminated to the trauma and orthopaedic surgery community via presentations at national and international meetings, as well as publication in peer reviewed journals.

The results will be made available to patients and the public via newsletters, press releases and blogs.

The trial design and report aim to be of sufficient quality to inform policy such as NICE guidance.

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### Author Contribution:

- A. L. Sims, Protocol development, trial management, writing the paper.
- N. Parsons, Design of study and writing of paper.
- J. Achten, Protocol development, trial management, manuscript write-up.
- X. L. Griffin, Project conception, writing and proof reading manuscript.
- M. L. Costa, Data analysis and writing the paper.
- M. R. Reed, Study design, paper editing.

### ICMJE conflict of interest:

- None declared.

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