

BMJ Open Randomised controlled trial of the sliding hip screw versus X-Bolt Dynamic Hip Plating System for the fixation of trochanteric fractures of the hip in adults: a protocol study for WHiTE 4 (WHiTE4)

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ABSTRACT

Introduction Sliding hip screw fixation is well established in the treatment of trochanteric fractures of the hip.

The X-Bolt Dynamic Hip Plating System builds on the successful design features of the sliding hip screw but differs in the nature of the fixation in the femoral head. A randomised pilot study suggested that the X-bolt Dynamic Hip Plating System might provide similar health-related quality of life while reducing the risk of revision surgery when compared with the sliding hip screw. This is the protocol for a multi

centre randomised trial of sliding hip screw versus X-Bolt Dynamic Hip Plating System for patients 60 years and over treated for a trochanteric fracture of the hip.

Methods and analysis Multicentre, multisurgeon, parallel, two-arm, randomised controlled trial. Patients aged 60 years and older with a trochanteric hip fracture are potentially eligible. Participants will be randomly allocated on a 1:1 basis to either sliding hip screw or X-Bolt Dynamic Hip Plating System. Otherwise, all care will be in accordance with National Institute for Health and Care Excellence guidance. A minimum of 1128 patients will be recruited to obtain 90% power to detect a 0.075-point difference in EuroQol-5D health-related quality of life at 4 months postrandomisation. Secondary outcomes include mortality, residential status, revision surgery and radiographic measures. The treatment effect will be estimated using a two-sided t-test adjusted for age, gender and cognitive impairment based on an intention-to-treat analysis.

Ethics and dissemination National Research Ethics Committee approved this study on 5 February 2016 (16/WM/0001). The study is sponsored by the University of Oxford and funded through an investigator initiated grant by X-Bolt Orthopaedics. A manuscript for a high-impact peer-reviewed journal will be prepared, and the results will be disseminated to patients through local mechanisms at participating centres.

Trial registration number ISRCTN92825709.

BACKGROUND

Due to an increasing incidence, hip fractures now place a very large burden on current

Strengths and limitations of this study

- Pragmatic, multicentre, multisurgeon randomised controlled trial.
- Includes all participants over 60 years of age, including those with chronic cognitive impairment.
- Reports the UK core outcome set for hip fracture.
- Powered to detect differences in health-related quality of life.
- Not designed to detect differences in risk of failure of fixation.

healthcare systems. Approximately 1.5% of the total healthcare budget in established market economies is currently spent on the care of patients sustaining a hip fracture.¹ Research focusing on optimising current treatment pathways and assessing new treatment options in this clinical area is crucial.

Hip fractures can be subdivided into intracapsular and extracapsular fractures. Approximately half of all hip fractures are extracapsular, and the great majority of these are trochanteric fractures, that is, a fracture in the region between the greater and lesser trochanter.² The rationale for fixation of these fractures relies on controlled collapse at the fracture site allowing bone ends to compress and union to occur before potential metalwork failure.

Sliding hip screw (SHS) fixation is well established in the treatment of extracapsular fractures, and in many fractures, SHS is effective at allowing controlled collapse of the fracture with consequent mechanical stability leading to healing of the fracture.³ However, in some hip fractures, there is deficient bone to share load with the fixation device. Rather than controlled collapse along the line of the

screw, the screw may cut out from the head of the femur leading to failure of the fixation and damage to the hip joint.⁴ Revision surgery, to either refix or replace the proximal femur, is complex, and the outcomes are poor in this frail group of patients.⁴

The X-Bolt Dynamic Hip Plating System (XHS) builds on the successful design features of the SHS by having a plate attached to the lateral femur and a single telescoping screw in the femoral head but differs in the nature of the fixation in the head. Expanding flanges are deployed to engage and compress the surrounding cancellous bone improving fixation.⁵ Trochanteric fractures rely on the quality of fixation in the femoral head to prevent cut out, and the poor bone quality encountered in the patients sustaining these fractures is often a contributor to failure. Our pilot work has demonstrated that there may be a reduced risk of revision using the XHS compared with the SHS.⁶

This is the protocol for a multicentre, multisurgeon, parallel, two-arm, randomised controlled trial. This trial protocol is based on the trial protocol for the pilot trial.⁷ This trial will be embedded within the World Hip Trauma Evaluation Comprehensive Cohort Study.⁸ The study will include a two-way superiority comparison between XHS and SHS.

Objectives

The objectives of WHiTE 4 trial are to quantify and draw inferences on the observed differences:

- ▶ in participants' health status between the trial treatment groups at 4 months post surgery.
- ▶ in the risk of all cause revision surgery within the first year post surgery between the trial treatment groups.
- ▶ in participants' health and functional status between the trial treatment groups at 12 months post surgery.

METHOD AND ANALYSIS

Eligibility

Patients will be screened in seven large National Health Service (NHS) Trusts in the UK against the following criteria:

Inclusion criteria

Patients presenting with trochanteric fracture of the hip who in the opinion of the treating surgeon would benefit from SHS fixation.

Exclusion criteria

1. Patients younger than 60 years of age.
2. Patients with a subtrochanteric fracture.
3. Patients who are managed non-operatively.

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 the majority of patients find the initial period of their treatment in

hospital confusing and disorienting. 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 surgery (where possible) and informing the patient and any next of kin about immediate clinical care. It is often not possible for the patient or relative/carer (consultee) to review trial documentation, weigh the information and communicate an informed decision about whether they would wish to participate. The consent procedure for this trial will reflect that of the surgery, with the clinical team assessing capacity before taking consent for the surgical procedure, and this capacity assessment then being used to decide on the proper approach to consenting to the research. An appropriate method, in line with the mental capacity act and approved by a National Research Ethics Committee, will then be used to gain either prospective or retrospective consent from the patient or appropriate consultee by a Good Clinical Practice (GCP)-trained, appropriately delegated member of the research team.

Randomisation and blinding

Allocation sequences will be generated at random by the trial statistician. Allocation will be assigned using secure, online randomisation via a distant computer generated system administered by Oxford Clinical Trials Research Unit, University of Oxford. Participants will be enrolled by the operating surgeon or trial research associates. Participants will be assigned to their treatment allocation before surgery.

The treatment allocation will be stratified by trial centre. The surgery will be performed under the care of any of the consultant surgeons in the collaborating centres. The large number of surgeons—previous experience in similar trials suggests over 200 surgeons will take part—and the wide skill mix should eliminate any 'surgeon effect' such that stratification by surgeon is not required. In order to negate bias in the self-reported health-related quality of life (HRQoL) outcome measures (Euro-Qol-5D-5L (EQ-5D-5L)), participants will be blinded to the treatment allocation. The operating surgeon cannot be blinded to the allocation and will take no part in the assessment of the trial outcomes. 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.

Treatments

Standardised treatment pathway

Participants will usually be assessed in the emergency department. Diagnosis of a fracture of the proximal femur 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.

A regional or general anaesthesia technique will be used for every participant. Perioperative analgesia will be achieved by combining a local anaesthetic nerve block (femoral and lateral cutaneous nerve of the thigh, fascia iliaca or lumbar plexus) using either a nerve stimulator or ultrasound-guided technique, periarticular anaesthetic infiltration, intravenous paracetamol 1g intravenous infusion and opiate analgesia as clinically indicated.

All participants will have an attempted closed reduction of their fracture. The lower limb will be supported on a fracture table. Internal fixation with either device will be performed following the manufacturer's guidelines. Postoperative analgesia will be prescribed intraoperatively and reviewed by the responsible clinical teams as appropriate. In the postoperative period, as per standard of care, participants will undergo an initial physiotherapy and occupational therapy trauma assessment. A full social, cognitive, premorbid function and falls history will be obtained and documented. Participants will be given the relevant NHS Trust Patient Information packs. An initial treatment plan with objectives will be made, recorded and commenced. The aim of this plan will be for participants to mobilise through early, active, full weight bearing. Participants will be discharged from the acute orthopaedic trauma ward at the earliest safe opportunity to the most appropriate discharge destination as determined by the multidisciplinary clinical team.

Allocated treatments

Participants will be randomly allocated to one of two groups:

1. SHS.
2. XHS.

Group 1: SHS

Fixation will involve a SHS with a plate as long as the surgeon feels necessary to achieve adequate fixation in the femoral shaft. The use of supplementary fixation such as wires, cables, lag screws and trochanteric stabilisation plate attachments is permitted at the surgeon's discretion.

Group 2: XHS

Fixation will involve an XHS used in accordance with the manufacturer's guidelines. Similar to the SHS group, the length of the plate will be at the surgeon's discretion. Supplementary fixation with wires, cables and lag screws are also permitted at the surgeon's discretion.

Outcomes

Personal data collected during the study will be handled and stored in accordance with the 1998 Data Protection Act, which requires data to be anonymised as soon as it is practical to do so.

The study databases will be set up by the computer programmer, and all specifications agreed between the computer programmer, statistician and trial manager and other relevant members of the trial team. The procedure for data entry will be documented in the data management plan.

The data collected from participants will be entered in linked-anonymised form to the trial database. Any paper copies of identifiable data, and corresponding reidentifying links to the participant trial ID, will be stored separately, in a locked cabinet in an access-restricted part of the University of Oxford. Names and addresses will not be disclosed to anyone other than staff involved in running the study. Direct access to source data/documentation may be required for study-related monitoring or audit by the sponsor, regulatory authorities, NHS Trust R&D staff or ethics committees.

As per routine clinical care, the existing National Hip Fracture Database dataset will be collected via telephone interview or postal questionnaire. We propose to augment this to include those outcomes reported from the UK consensus for a hip fracture core outcome set.⁹ Additional data recorded will be radiographic fracture pattern obtained from routinely collected X-rays and EQ-5D-5L at baseline (retrospective prefracture), 4 and 12 months postfracture. Four months represent a routine follow-up point for the National Hip Fracture Database and the point at which recovery following hip fracture plateaus. Parsons *et al*¹⁰ reported that EQ-5D improved after surgery to around 4 months, with little evidence for subsequent improvement after this time-point. However, complications and potential revisions will need to be reviewed up to a minimum of 1 year postsurgery. In addition, longer term follow-up to 12 months is recommended by the Medical Research Council for investigations of all complex interventions.¹¹ Copies of the participants' routine 'operation note' and 'discharge summary' will be collected from their medical notes. The discharge summary includes details of their treatment, perioperative complications and discharge address.

Primary outcome measure

EQ-5D-5L 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.¹² An updated version of the EQ-5D with five response levels, the EQ-5D-5L, has recently been developed to enhance the responsiveness of the instrument to changes in patient health. The measurement properties of the EQ-5D in this patient population have been extensively investigated and is currently the best measurement tool available.^{10 13} This outcome will be obtained through telephone interview with the participant or consultee.

Secondary outcome measures

These will include:

1. *mortality*, which is obtained from patients' medical notes;
2. *functional status* will be assessed in line with NHFD requirements. This will include walking ability indoors and outdoors and information regarding residential status; obtained through patient interview/questionnaire;

3. *revision surgery and cause*, which is obtained from patients' medical notes';
4. *complications*, which is obtained from patients' medical notes;
5. *radiographic outcomes, including screw migration and cut out*, which is collected from any X-rays taken as part of standard clinical follow-up during the first 12 months post surgery.

Sample size

The best available evidence we have from data collected during the WHiT and WHITE studies suggests that the SD for EQ-5D at 4 months postsurgery is approximately 0.3 points.⁹ The best available evidence for what constitutes a minimal clinically important difference (MCID) for EQ-5D that is worth detecting comes from a review of MCID estimates.¹⁴ After reviewing the literature, they estimated a median value of 0.08 for the MCID for EQ-5D-3L. Using a conservative estimate of the standard deviation (SD=0.33), this suggests a standardised effect size of approximately 0.24, a 'small to moderate effect' based on Cohen's criteria.¹⁵ Taking a conservative approach, we considered three possible target different values of 0.07, 0.75 and 0.08.

Assuming that the EQ-5D-3L at 4 months postsurgery has an approximate normal distribution, which Parsons *et al*¹⁰ suggests is reasonable, and a 1:1 allocation ratio, then if the true difference between the experimental and control group EQ-5D means is in the range 0.07–0.08, 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) [table 1](#).

Taking the intermediate MCID of 0.075, for 80% (90%) power, we would need to recruit 253 (338) patients in both the experimental arm and in the control arm, 506 (676) in total. In this population, we expect considerable loss to follow-up due mainly to patients declining consent to further follow-up and incapacity, so we have assumed that only 60% of recruited study participants will be available at the definitive endpoint at 4 months. This gives a total sample size of 844 for 80% power and 1128 for 90% power. Conservatively, we aim to recruit 1128 to ensure 90% power based on these assumptions.

Statistical analysis

The principal analyses will be conducted on an 'as allocated' basis irrespective of compliance. Two-sided 5% significance level will be adopted and corresponding 95%

CI's will be calculated whenever possible. The primary outcome measure, EQ-5D-5L at 4 months post surgery, will be analysed by calculating the adjusted treatment effect by using linear regression to compare the EQ-5D-5L score at 4 months (with a zero value imputed for those who died by this time point) between the treatment arms, adjusting for age, gender and cognitive impairment.

A sensitivity analysis of EQ-5D-5L score at 4 months with adjustment for the retrospective baseline EQ-5D-5L score in addition to age, gender and cognitive impairment will also be performed to enable the influence of this factor to be evaluated. Additionally, a two-sided t-test for differences between SHS (control) and XHS will also be used to calculate an unadjusted treatment effect both for EQ-5D with and without zero for those who died. Some outcome data are likely not to be available due to lack of completion of individual data items, declining consent for further follow-up or general loss to follow-up. Where possible, the reasons for data 'missingness' will be ascertained and reported. The nature and pattern of the 'missingness' will be carefully considered, including in particular whether data can be treated as missing completely at random. Missing data may be imputed in sensitivity analyses if considered beneficial to the interpretation of the main findings. Any imputation methods used for scores and other derived variables will be carefully considered and justified. Reasons for ineligibility, non-compliance, withdrawal or other protocol violations will be stated and any patterns summarised.

Secondary measures will be analysed using generalised linear models with adjustment for centre, baseline EQ-5D-5L, age, gender and cognitive impairment as appropriate. EQ-5D-5L at 12 months will be analysed with the same sensitivity analyses as the primary outcome. Data will be summarised with point estimates of mean and SD, 95% CI's, or proportion and risk ratios. Differences between SHS and XHS will be analysed using a two-sided significance level of 5%.

The number and temporal pattern of adverse events will be investigated to assess if these differ between treatment groups.

Trial oversight

The day-to-day management of the trial will be the responsibility of the clinical trial manager, based at Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences and supported by the Oxford Clinical Trials Research Unit (OCTRU) staff. This will be overseen by the Trial Management Group, who will meet monthly to assess progress. It will also be the responsibility of the clinical trial manager to undertake training of the research associates at each of the trial centres. The trial statistician will be closely involved in setting up data capture systems, design of databases and clinical reporting forms.

A Trial Steering Committee (TSC) and a Data & Safety Monitoring Committee (DSMC) will be set up. The study DSMC will adopt a DAMOCLES charter, which defines its

Table 1 Group sizes required following sample size calculation based on varying assumptions.

Power (%)	MCID		
	0.07	0.075	0.08
80	290	253	222
90	387	338	297

terms of reference and operation in relation to oversight of the trial. They will not be asked to perform any formal interim analyses of effectiveness. They will, however, see copies of data accrued to date or summaries of that data by treatment group, and they will assess the screening algorithm against the eligibility criteria. 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 TSC at any time if, in their view, the trial should be stopped for ethical reasons, including concerns about participant safety. DSMC meetings will be held at least annually during the recruitment phase of the study.

Quality control

The study may be monitored or audited in accordance with the current approved protocol, relevant regulations and standard operating procedures by the host organisation, sponsor or appropriate regulatory authorities. A monitoring plan will be developed according to OCTRU standard operating procedures, which involve a risk assessment. The monitoring activities are based on the outcome of the risk assessment and may involve central monitoring and site monitoring.

Ethics and dissemination

A manuscript for a high-impact peer-reviewed journal will be prepared. Authorship will be determined in accordance with the ICMJE guidelines, and other contributors will be acknowledged. The results of this project will be disseminated to patients through local mechanisms at all participating centres.

Contributors XLG, MLC and JA developed the trial protocol and contributed to the writing of the manuscript. XLG is the chief investigator. WS developed the statistical analysis plan and is leading the statistical analysis for the study. JC developed the analysis plan and contributed to the reporting plan for the study. He is providing statistical oversight to the study.

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Disclaimer The views expressed are those of the authors.

Competing interests None declared.

Patient consent Obtained.

Ethics approval National Research Ethics Committee – West Midlands.

Provenance and peer review Not commissioned; externally peer reviewed.

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