

**Stabilisation of unstable pertrochanteric hip fractures: A feasibility
randomised control trial comparing Endovis proximal femoral nail vs
Dynamic Hip Screw**

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Abstract

There is still no consensus on the best fixation device for unstable pertrochanteric (i.e. AO/OTA 31A2) fractures. Interestingly, a third of patients with hip fractures have a degree of cognitive impairment and are usually excluded from relevant randomised trials.

The aim of this study was to assess the feasibility of performing a randomised control trial including patients with and without cognitive impairment and to compare intramedullary nail and Dynamic Hip Screw (DHS) for the fixation of unstable pertrochanteric fractures.

The abbreviated mental Test Score (AMTS) was used to screen for dementia. The Timed Up and Go (TUG) test was used as the primary outcome measure. Peri-operative parameters, patient-reported outcomes and radiographic parameters were used as secondary clinical outcomes. Patients were followed-up at 2, 4 and 12 weeks.

Although it was feasible to recruit 60 patients, retention rates were lower than expected, especially among patients with dementia. Moreover, the TUG test proved was not a suitable tool to be used as a functional outcome measure; high proportion of patients were not able to perform it even at 12 weeks.

There was preliminary evidence of treatment effect in pain assessment at 2 weeks and radiographic outcomes at all time points in favour of the nail group.

In conclusion, it is feasible to perform an RCT including patients with and without dementia, but high levels of attrition are to be expected. The Timed Up and Go test was not a suitable tool to be used in this population. Fixation with a nail appeared to be advantageous to fixation with a DHS in terms of early pain levels and radiographic outcomes.

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Abbreviations

| | | | |
|-------------------|--|-----------------|------------------------------------|
| AO | Arbeitsgemeinschaft für Osteosynthesefragen | Hb | Haemoglobin |
| AP (X-ray) | Antero-posterior (X-ray) | HHS | Harris Hip Score |
| AMTS | Abbreviated Mental Test Score | HRA | Health Research Authority |
| ASA | American Society of Anesthesiologists | InterTan | Intertrochanteric antegrade nail |
| CCI | Charlson Comorbidity Index | KCTU | Kings Clinical Trials Unit |
| CI | Confidence Interval | LEM | Lower Extremity Measure |
| CRF | Case Report Form | LOS | Length of stay |
| CT | Computed Tomography | LHS | The London Handicap Scale |
| CTCAE | Common Terminology Criteria for Adverse Events | MMSE | Mini-Mental State Examination |
| CTIMP | Clinical Trial of an Investigational Medicinal Product | NA | Non applicable |
| DUR | Days until ready (for discharge) | NHFD | National Hip Fracture Database |
| DEMQOL | Dementia Quality of Life | NHS | National Health System |
| DHS | Dynamic Hip Screw | NRS | Numeric Rating scale |
| DNA | Did not attend | OR | Odds ratio |
| EQ-5D | Euroqol-5-dimensions | OTA | Orthopaedic Trauma Association |
| FIM | Functional independence Measure | PFNA | Proximal femoral nail antirotation |
| GCP | Good Clinical Practice | PROMs | Patient-Reported Outcome Measures |
| GDS | Geriatric depression scale | Pt | Patient |
| | | R&D | Research and Development |
| | | RCT | Randomised control study |
| | | REC | Research Ethical Committee |

| | |
|-----------------|--|
| RUSH | Radiographic Union Score for Hip |
| SF-36 | Short Form 36-item health survey |
| SHS | Sliding Hip Screw |
| TUG test | Timed Up and Go test |
| TAD | Tip-apex distance |
| TFN | Titanium Trochanteric Fixation Nail |
| SAE | Significant adverse event |
| VAS | Visual Analogue Scale |
| 2MWT | 2-minute walk test |

Chapter 1

Epidemiology and classification of proximal femoral fractures

1.1 Epidemiology of proximal femoral fractures

Proximal femoral fractures, or most commonly known as hip fractures, are considered a worldwide epidemic (1). Due to an increasing aging population, hip fractures are expected to increase in coming years. Specifically, the number of hip fractures is estimated to increase from 1.6 million in 1990 to 4.5 million in 2050 (2). Hip fractures are typically a result of low energy injuries in elderly frail people. These injuries usually result from falls from standing height in elderly osteoporotic patients with multiple comorbidities.

Noteworthy, the annual incidence of hip fractures varies in different countries. The incidence of hip fractures in adults >50 years old in the UK is 224 per 100,000 people per year (113 per 100,000 for men and 321 per 100,000 for women) (3). Similar incidence has been reported in Italy (334 per 100,000 people per year), in Netherlands (288 per 100,000 people per year) and Spain (228 per 100,000 person per year) (3). On the contrary, incidence of hip fractures is the highest in Scandinavian nations and North America; Sweden has an incidence of 390 per 100,000 people per year for men and 830 per 100,000 per year for women (4) whereas the incidence of hip fracture in the USA is 741 per 100,000 per year (5). Although a third of hips fractures worldwide occur in Asia, the incidence of hip fracture is lower than that in the west countries; China has an incidence of 136 per 100,000 (2) and South Korea has an incidence of 181 per 100,000 per year (6). Although these differences are considerable, the reasons of this geographical variation are not well understood. Possible explanation may involve the level of urbanization of the country, sun exposure and the socioeconomic status of the country (1).

Although the number of patients with hip fractures increases with time, the incidence of hip fractures has decreased in the recent years. Two big epidemiologic studies from the USA have shown that the incidence of hip fractures in people older than 70 years old has been decreasing since 2000 (7,8). Despite the initial increase in the incidence observed between 1986 and 1995, there has been a steady 20-25% decrease in incidence from 1995 onwards. This decrease is coincident with the increase in the use of antiresorptive therapies; however, this change cannot be attributed solely to bisphosphonate treatment. Lifestyle changes such as avoidance of smoking, regular physical exercise, moderating alcohol consumption and fall awareness have also contributed to this decrease. Overall, public and physicians education and

awareness on fragility fractures and osteoporosis has increased in the last 25-years and this is also considered a factor towards the decrease in the incidence of hip fractures (7).

Age and sex

The average age of patients with hip fracture in the UK is 83 years for women and 84 years for men (9). Seventy-six per cent of these fractures occur in women. The majority of fractures occur between the ages of 75 and 84 (7). Only around 16% of patients with hip fracture are 75 years old or younger. The overall number of people with hip fractures older than 85 years old is steadily increasing in the most recent years and in future most patients with hip fractures may be 85 years of age or older. It is estimated that the risk of hip fracture is 18 times higher for women over 85 years old and 32 times higher for men over 85 years old than women and men aged 65-69 years old respectively (8).

Race/ethnicity

Caucasians and northern Europeans have higher incidence of hip fractures than other ethnicity groups (1,8,10). In contrast, native Americans have the lowest risk of sustaining a hip fracture. The reasons of these big differences are not well understood. Lifestyle differences have been suggested as potential reason, but these factors have not been assessed in epidemiological studies yet.

Mortality

Hip fractures are associated with high mortality. However, since 2007 there has been a slight decrease in mortality rates (11). In the UK, the 30-day mortality has decreased from 8.3% in 2010 to 6.1% in 2019; a 2% decrease in mortality between 2010 and 2019 in the UK, means that more than 1,300 people remain alive 30 days post-surgery per year. The main reasons for this decrease include the improvements in the care of patients with hip fractures in the last two decades. More specifically, the introduction of a multidisciplinary approach in the care of patients with hip fractures, surgery within 36 hours from admission, standardisation of type of surgery depending on the type of the fracture, effective analgesia are the main changes in practice in the UK in the last decade that have led to better clinical outcomes and decreased 30-day mortality. There has been a similar decrease in mortality in the USA; 30-day mortality has decreased from 5.9% to 5.2% for women and from 11.9% to 9.3% for men between 1986 and 2004 (7). However, one-year mortality continues to be high; mortality rates at 1 year vary from 20% to 32% (7,9).

Risk factors

According to NICE, hip fractures are 'fragility' fractures caused by a fall from standing height or less, affecting older people with osteoporosis or osteopenia (9). Apart from osteoporosis, smoking, medical comorbidities, general health status, exercise and socioeconomic status are recognized risk factors for hip fractures (8). A systematic review has identified 12 predictors associated strongly with mortality in patients with hip fractures. These predictors include >80 years of age, male gender, care home as pre-injury residence, poor pre-injury walking capacity, poor activities of daily living, ASA score 3 and 4, multiple comorbidities, cognitive impairment, poor mental state, diabetes, cancer and cardiac disease (12).

1.2 Impact of patients with hip fracture on the health care system

Hip fractures are considered a major public health issue not only because of the large number of people who sustain a hip fracture annually but also because of the associated costs. The overall cost of hip fractures is around £2 billion in the UK (9) and \$17-20 billion in the USA (8). With an average length of stay in an acute bed of 15 days, it is estimated that more than 4,000 beds are occupied daily by patients with hip fractures throughout the NHS (11). Moreover, only 50% of the patients who have been admitted from their own home will be able to be discharged back to the same destination. The rest will require further rehabilitation or assisted accommodation for long-term and this explains the high costs spent in the aftercare. Finally, 26.8% of the patients with hip fracture will require further surgery within the first year (11). Overall, it is clear that hip fractures are life changing events for the individual and a big burden for the healthcare system.

1.3 Hip fractures in patients with dementia

Definition of dementia

Dementia is a term to describe decline in cognitive function. Symptoms of dementia include memory loss, problems with reasoning, communication, change in personality, and difficulty in performing everyday activities. It is a progressive condition and symptoms vary from person to person. The most common type is Alzheimer's disease; other types include vascular dementia, dementia with Lewy bodies, frontotemporal dementia and mixed dementia.

According to WHO, there are around 50 million people with dementia worldwide and 10 million new cases every year (13). Dementia is one of the major causes of disability and dependency in older people. The

total cost of dementia in the UK, including health care and social care costs, is estimated to be £26.3 billion (14).

Cognitive impairment, similarly to dementia, is a condition characterised by memory problems, difficulties in speech and decision making. However, the main difference with dementia is that it is not as severe as dementia and symptoms don't cause any interference with the person's daily activities.

For the purposes of this study, cognitive impairment and dementia will be considered as one condition.

Diagnosis

There is no specific test to diagnose dementia. Initial suspicion of the condition usually arises while taking a history. Exploring cognitive, behavioural and psychological symptoms will reinforce the suspicion. The first objective is to exclude reversible causes of cognitive decline such as infection, delirium, tumour, and intracranial bleeding.

Further investigations for dementia include cognitive tests. NICE recommends the use of the following tests: the 10-point cognitive screener, the 6-item cognitive impairment test, the 6-item screener, the memory impairment screen, the mini-cog and 'Test your memory' test (14).

The most used test to screen for dementia is the Mini-Mental State Examination (MMSE). It consists of 30 questions that assess orientation, memory, language, attention and visuospatial awareness. It takes approximately 10min to be completed. Scores range from 0-30. Scores lower than 24 are indicative for dementia. MMSE is considered to have a sensitivity of 0.81 and specificity of 0.89 for the diagnosis of dementia (15).

Other screening tests include the Abbreviated Mental Test Score (AMTS). This is a 10-question score. Maximum score is 10 and scores lower than 8 are indicative for dementia or delirium. The AMTS, similarly to MMSE, assesses orientation, memory and attention. The AMTS is freely available and it has comparable to MMSE sensitivity and specificity (sensitivity 0.88, specificity 0.85) (15).

The MMSE used to be the gold standard screening tool for cognitive impairment and dementia; however due to copyright issues, its use has declined in the recent years and other tests to assess cognition have become more popular (15). The AMTS is quick to perform and freely available and it is the standard cognitive assessment that every elderly patient with a hip fracture has when admitted in the hospital in the UK.

Dementia in hip fracture patients

Thirty per cent of patients with hip fractures have a degree of cognitive impairment (9). Dementia is a recognised risk factor for sustaining a hip fracture but also it is associated with higher morbidity and mortality (12).

The 2016 annual National Hip Fracture Database report described the implications of dementia in patients with hip fractures (16). Patients with dementia have twice higher risk of in-hospital death than patients without dementia (in hospital mortality: 9.5% vs 4.6%). Moreover, patients with dementia are more likely to stay for nearly 5 days longer in hospital than patients without cognitive impairment (hospital stay: 22.8 vs 18.1 days). Patients with low AMTS are less likely to be mobilised by the first postoperative day (72.2% vs 82.1%), and they are half as likely to return to their own residence within 30 days (30.5% vs 58.1%). Overall, patients with cognitive impairment are expected to have slower rehabilitation and significantly higher mortality following a hip fracture.

1.4 Patients with dementia and clinical trials

Clinical trials are important in creating evidence that clinical practice can be based on. Including patients with dementia in clinical trials is challenging. If the patient hasn't got the capacity to understand and retain the information about a study and to make an informed decision, then they can't consent for any treatment as well as for any participation in a research project. Moreover, patients with dementia have difficulties in expressing their feelings or answering specific questions. Therefore, it may be impossible for them to follow instructions and complete specific physical assessment tests or to answer a questionnaire assessing physical ability or quality of life. Finally, it is difficult to arrange follow-up visits for patients with dementia since they depend on their carers for any transports or any other everyday activities.

Since a third of the patients with hip fractures have a degree of cognitive impairment, it is important to include this patient-group in clinical studies. Excluding these patients introduces a selection bias and reduces the external validity of the study.

A recent systematic review has shown that 8 out of 10 clinical trials on hip fractures exclude or ignore patients with cognitive impairment (17). As a result, current evidence comes from studies mainly based on patients without cognitive impairment and it is unknown whether the current known outcomes apply to this subpopulation with cognitive impairment.

The above applies for RCTs on intertrochanteric fractures as well. More specifically, a large meta-analysis on intertrochanteric fractures comparing intramedullary and extramedullary fixation devices included in

total 43 RCTs; only 10 of those (23.3%) included patients with cognitive impairment (18). Similarly, in a meta-analysis comparing intramedullary vs extramedullary fixation but only focusing on AO/OTA 31A2 fractures, only one study (16.7%) clearly reported that patients with dementia were included (19).

Overall, it can be said that the current RCTs exclude in their big majority patients with cognitive impairment since less than a quarter of them in the best-case scenario include this subpopulation. However, it is essential that clinicians and researchers make their best to include patients with and without cognitive impairment in clinical trials to minimise the risk of selection bias and also to produce evidence that applies to all patients with hip fractures.

1.5 Patient reported outcome measures in hip fracture trials

Selecting appropriate outcome measures is essential when designing clinical trials which compare clinical effectiveness between different fixation devices. Traditionally, outcome measures on studies on proximal femoral fractures have included clinical parameters such as mortality, success of surgical interventions and complications (20,21). Although, these parameters are very important for the patients and for the surgeons, they don't occur in all the subjects (such as complications and mortalities) or they are observed very rarely (such as specific complications, i.e. screw cut-out). Recently there has been a shift from clinical outcomes to patient reported outcome measures (PROMs) as primary or secondary assessment tools (22–24). Patient reported outcomes are questionnaires that collect information about patient's symptoms, health condition, function or quality of life directly by the patients and this information is not interpreted by a clinician or anyone else (25). They provide direct information on what patients consider important but also, they assess what the patients are capable of doing in their normal life rather than in a clinic room. On the contrary to complications and mortality, PROMs can be collected by every eligible patient and as a result comparisons are easier to be made.

Despite the overall increase in the use of PROMs in clinical research, a recent systematic review has reported that there is no specific PROM for patients with hip fractures and further research is required in the development of the 'best' measure for this diverse and growing patient group (26). The majority of the measures that have been used in current hip fracture trials have not been evaluated adequately for this patient group. The reliability, validity, and responsiveness of the most commonly used PROMs has been evaluated in the general population or in patients with other specific conditions but not in patients with hip fractures (26).

With regard to the studies on intertrochanteric fractures, a recent meta-analysis found that quality of life and functional status are under-reported in randomised control trials (18). The main reason for this was poor data completeness as most of the studies did not report data at baseline or any change from baseline. It was concluded that it is uncertain whether quality of life is improved following surgical treatment of hip fractures (18). Another recent meta-analysis reported that it was not possible to compare different functional outcome scores across the studies due to the lack of comparable measures (27).

In summary, although PROMs may be better outcome measures than clinical outcomes (i.e. mortality and complications) in clinical research, current randomised trials on intertrochanteric fractures either do not include such outcomes or use a wide variety of measures (validated or not for this type of population) and as a result no comparisons across the studies are possible.

1.5.1 Types of Patient Reported Outcome Measures

Patient reported outcome measures can be divided in the following categories: 1. general quality of life; 2. activities of daily living; 3. mobility and physical performance; 4. disease specific and 5. hip specific.

General Quality of Life measures:

The Short Form 36-Item survey (SF-36) is a general measure of quality of life. It consists of 36 items that explore the health of the patient in the previous 4 weeks. Areas covered include physical function, vitality, pain, general health, social function, emotional function, and mental health. SF-12 is a shorter version of SF-36. It is the most commonly used measure in hip fracture studies (26) and it has been shown to be reliable and valid for this patient group (28,29).

The EuroQol or EQ-5D is a general quality of life measure that evaluates the general quality of life of a patient. It consists of two parts; the first part consists of 5 questions on mobility, self-care, daily activities, pain and depression. The second part consists of a 100-point visual analogue scale and patients are asked to rate their overall health on the 100-point scale. It is a valid and responsive tool in assessing general health related quality of life in patients with hip fractures, including patients with cognitive impairment (30).

The Dementia Quality of Life (DEMQOL) questionnaire is a tool to assess health related quality of life in patients with cognitive impairment (31). It consists of two questionnaires; the first one is answered by the patient and it consists of 28 questions; the second one is answered by a caregiver and consists of 31 questions. The questionnaires cover 4 domains: emotion, memory, ability to carry out daily living

activities, and perception of overall quality of life. All questions are answered with the same 4-point Likert scale; (1= a lot, 2= quite a bit, 3= a little, 4= not at all). The higher the overall score, the better the health-related quality of life is. Although it is an accurate measure to assess quality of life in patients with cognitive impairment (32), its use has been very limited in the literature and it has not been validated yet in patients with hip fractures.

Activities of daily living

The Functional Independent Measure (FIM) is a measure of disability; an interviewer asks a patient how much able they are to perform activities of daily living including self-care, sphincter control, transferring, locomotion, communication, and social interaction and cognition. Each activity is rated from 1-7 (1=totally unable, 7=totally independent). Although it has been initially used in patients participating in rehabilitation programmes, it has been shown to be a reliable measure to assess the level of disability in patients with proximal femoral fractures (33). However, it has poor correlation with mobility scores and it is not considered a specific measure of functional mobility in patients with hip fractures (34).

The Barthel Index measures the ability of a patient to perform specific activities of daily living. It consists of 10 items; each item describes a specific function such as feeding, bathing, continence, mobility and dressing and each function is scaled from 0-10 (0=unable to perform, 10=independent to perform). Barthel index has been validated in patients with hip fractures following hip hemiarthroplasty and it has been shown to be a good measure to assess functional recovery (35).

The Functional Recovery Score is an 11-item questionnaire that assesses the ability of a patient to perform activities of daily living and mobility. Each item is rated between 0 and 4 (0=cannot do activity at all, 4=no help needed). It was designed for use specifically in patients with proximal femur patients and it has been shown to have good validity and reliability in assessing functional mobility (36). However, it is not widespread and it has only been used in a handful of studies (21).

The Lower Extremity Measure (LEM) is a 29-item questionnaire which assesses the ability of a patient to perform physical activities inside and outside their place of residence. Each area is rated from 0 to 4 (0=extremely difficult or unable to perform, 4=no difficulty). The higher the score is, the better the physical function to be expected. Similarly, to other PROMs, it has been validated and it is sensitive to change of functional mobility in patients with hip fracture (37). Contrary to the FIM, it is considered a specific measure of mobility in patients with hip fractures.

Mobility and physical performance:

The Timed Up and Go test (TUG) is a physical performance test that measures the time taken for a patient to stand up from a seated position, walk three meters, turn around, walk back to the chair and sit down. It is a simple and objective measure used in the elderly and frail people to assess functional mobility (38). It has been validated in orthopaedic patients to evaluate their progress in rehabilitation programmes (39) and also in community-dwelling patients following hip fractures as a predictor of falls (40). However, there is very limited and mixed evidence for its validity in functional mobility in patients with hip fractures. A study including patients with intracapsular displaced fractures and excluding patients with cognitive impairment found that the TUG test at 3 weeks was a good predictor of independent (i.e. no walking aids) walking at 2 years and correlated well with the Lower Extremity Measure at 1 and 2 years (41). On the other hand, a study which analysed a cohort of patients recruited for an RCT, with trochanteric and subtrochanteric fractures and which included patients with cognitive impairment found that the post-operative TUG test on day 5 was not a suitable test to be used in this patient group due to the low percentage of patients who were able to perform it (42).

Although the TUG test is routinely used in patients with cognitive impairment, there is mixed evidence in the literature whether it is affected by patient's cognition status. Some studies have found that it has good test-retest reliability (43) and that it is not affected by the cognitive function (44) of the participants, whereas, other studies have found that TUG times have been higher in patients with cognitive impairment (45) and concluded that this test is infeasible in this patient group (46).

Overall, although the TUG test is a commonly used physical assessment tool in studies on hip fractures, the current literature is not clear whether it is affected by the cognitive function of the participants and, moreover, there is no clear evidence to suggest that it is a reliable measure to assess functional mobility; current literature has assessed it to be a good test to predict independent walking and falls.

The Parker and Palmer mobility score or the New Mobility Score is an assessment tool that assesses the ability of an individual to mobilise in the house, out of the house and to go shopping. Each of the 3 areas are scored from 0-3 (0=Not at all, 1= with help from another person, 2=with an aid, 3=No difficulty). It is considered a good predictor of mortality (47) and for regaining independency in mobility (48) after hip fracture. Although it is a measure developed for patients with hip fractures, it is most used as a pre-operative predictor rather than a functional mobility tool to assess recovery.

The London Handicap Score (LHS) is a measure of the disadvantaged experience due to ill health (49). It consists of 6 domains: mobility; physical independence; occupation; social integration; orientation;

economic self-sufficiency. Each domain has 6 levels, arranged in order of increasing disadvantage from “no disadvantage” to “most severe disadvantage”. It has been validated mainly in patients with chronic, multiple or progressive disease. It has found to be responsive to change at 3 and after 6 months following hip and knee replacement (50). However, it has not been validated yet in patients with hip fractures.

Hip specific scales

The Harris Hip Score (HHS) is an outcome measure which is completed by a clinician and assesses pain (1 item), function and activities (7 items), deformity and range of movement (4 items). The score has a maximum of 100 points. It has been validated in patients with osteoarthritis and it was found to be valid and responsive (51). However, it has not been validated in patients with hip fracture and it should be used with caution (26).

1.5.2 PROMS for patients with cognitive impairment

Finally, there has been little research on patient reported outcome measures in cognitive impaired patients with hip fractures. The majority of the studies excluded patients with cognitive impairment (26). Only the EQ-5D has been validated in this patient group (30); furthermore, the EQ-5D was found to be the same responsive as in patients without cognitive impairment. Further research is required to assess the validity and reliability of other patient reported outcome measures in cognitively impaired patients with hip fractures.

In summary, it is very important to choose the appropriate PROMs in trials that assess clinical effectiveness between two interventions. The current studies on hip fractures have used PROMs that are not designed or have not fully been validated for this patient group. There is lack in PROMs that are specific for this diverse group of patients with hip fractures and further research is required in developing more ‘ideal’ patient reported outcome tools. Future clinical trials on hip fractures should include patients with cognitive impairment and report outcomes specifically for this subgroup and, moreover, current PROMs need to be validated in patients with hip fractures with and without dementia.

1.6 Classification of proximal femoral fractures

Proximal femoral fractures include any fracture occurring between the tip of the femoral head and 5cm below the lesser trochanter (9). These fractures are widely known as hip fractures. They are subdivided into 2 main groups; intracapsular and extracapsular. Any fracture proximal to the insertion of the hip joint capsule is known as intracapsular fracture and any fracture distal to the insertion of the hip joint capsule is known as extracapsular fracture. This classification relates to the blood supply to the femoral head. The main blood supply of the femoral head in adults is through the capsular vessels along the joint capsule. Therefore, intracapsular fractures are more likely to be associated with compromise in the blood supply of the femoral head than extracapsular fractures. This is an important clinical factor as it determines the method of surgical treatment.

The intracapsular fractures are further subdivided into sub-capital and trans-cervical neck of femur fractures; the extracapsular fractures are further subdivided into basocervical, intertrochanteric and subtrochanteric fractures.

Intracapsular fractures (both sub-capital and trans-cervical fractures) involve the femoral neck. Undisplaced neck fractures are less likely to be associated with compromise of the blood supply of the femoral head and therefore these types of fractures can be fixed with internal fixation (i.e. screws). Displaced neck of femur fractures are highly associated with compromise of the capsular vessels and due to the high risk of complications (including non-union and avascular necrosis of the femoral head), these fractures are usually being treated with arthroplasty (i.e. hip replacement).

Depending on the location of the fracture line, extracapsular fractures can be basocervical, intertrochanteric or subtrochanteric. Basocervical fractures occur in the junction of the femoral neck and the femoral shaft and because they do not disturb the blood supply of the femoral head, these fractures are considered extracapsular and are being treated with the same principles as extracapsular fractures. Any fracture that occurs in the region between the greater and the lesser trochanter is known as intertrochanteric. Depending on the orientation of the fracture line, intertrochanteric fractures are further subdivided to stable and unstable; stable fractures extend from proximally and laterally to distally and medially whereas unstable fractures extend from proximally and medially to distally and laterally. The latter type of fractures is known as reverse oblique fractures. Moreover, stability depends on the comminution of the fracture; fractures with posteromedial comminution are also considered unstable. Stability of the fracture is important as it determines treatment. Lastly, fractures that occur at the level of the lesser trochanter and 5cm below are known as subtrochanteric fractures.

1.6.1 The AO/OTA Fracture and dislocation classification

Apart from the anatomical classification described above, there are other classification systems described in the literature. The most commonly used and complete classification system for any type of fracture is the 2018 AO/OTA (or OTA/AO) Fracture and Dislocation Classification Compendium (52). According to this classification, any fracture in the human skeleton has a unique fracture code which consists of two numbers followed by one letter followed by two numbers.

The first two numbers locate the bone and the affected segment in that bone. Every bone has a specific number; "1" is for the humerus, "2" for the forearm (2R for the radius and 2U for the ulna), "3" for the femur, "4" for the tibia (4F for the fibula), "5" for the spine, "6" for the pelvic ring and "7" for the carpus and hand.

The second number represents the location of the fracture in the bone. Every diaphyseal bone is divided in 3 segments; "1" is for the proximal segment, "2" for the middle segment, and "3" for the distal segment. The proximal and distal end segments are defined by squares; the side of this square is the widest part of the epiphysis or metaphysis of the bone. For humerus fractures, "4" and "5" are used for scapula and clavicle fractures respectively. For femoral fractures, "4" describes patella fractures. For tibia fractures, "4" is for malleoli (ankle) fractures. For the spine, pelvis and hand, a number describes a particular area of that specific bone (e.g. for spine, "1" is used for the cervical spine, "2" for the thoracic spine, "3" for the lumbar spine and "4" for the sacrum).

Following the two numbers there is a letter (A, B or C) which describes the morphology of the fracture. The description of the morphology of the fracture is different for diaphyseal fractures and end segment fractures (i.e. close to a joint). For diaphyseal fractures, "A" describes simple fractures (spiral, oblique, or transverse), "B" describes wedge type fractures (intact or fragmentary wedge) and "C" describes multifragmentary type fractures (intact or fragmentary segment). For end segment fractures, "A" describes extra-articular fractures, "B" describes partially articular fractures, and "C" describes complete articular fractures.

The proximal femur is an exception to the above rules. Fractures that involve the trochanteric area are type "A", fractures that involve the femoral neck are type "B" and fractures that involve the femoral head are type "C" fractures.

The last two numbers describe the fracture pattern further (e.g. for diaphyseal simple fractures, “1” is used for spiral, “2” for oblique and “3” for transverse fractures). These numbers are referred to as ‘groups’ and ‘subgroups’ of the fracture and are fracture specific.

Further to the unique fracture code, there are universal modifiers that describe further the morphology, displacement and associated injuries. These are optional and are added at the end of the fracture code within square brackets (52).

1.6.2 The AO/OTA classification for hip fractures (proximal end segment of the femur)

The AO/OTA classification divides the proximal femoral fractures in three types: Type A – extra-articular fractures around the trochanteric area, Type B – extra-articular fractures involving the femoral neck, Type C – articular fractures involving the femoral head.

Since this study focused on type A fractures, types B and C will not be described in further depth.

In the most recent version of AO/OTA classification system (2018), fracture classification of type A fractures has been significantly modified since the original fracture classification that was published in 1996. When this study was designed, the 1996 classification was available and therefore the ‘old’ classification system was followed. Moreover, all the published studies until today have uses the 1996 AO/OTA classification version. For simplicity, when AO/OTA classification is mentioned in the text of this manuscript, it will refer to the 1996 AO/OTA classification.

According to 1996 version of AO/OTA classification system (53), Type A proximal femoral fractures are divided in the following groups and subgroups (Figure 1):

- Group 1 - Simple 2-fragment intertrochanteric fractures:
 - 31A 1.1: The fracture line runs along the intertrochanteric line.
 - 31A 1.2: The fracture line runs through the greater trochanter.
 - 31A 1.3: The fracture line runs below the lesser trochanter.
- Group 2 – Multifragmentary pertrochanteric fractures:
 - 31A 2.1: With one intermediate fragment (lesser trochanter detached).
 - 31A 2.2: With two intermediate fragments.
 - 31A 2.3: With more than two intermediate fractures.

- **Group 3 – Intertrochanteric fractures:**
 - 31A 3.1: Simple reverse oblique.
 - 31A 3.2: Simple transverse.
 - 31A 3.3: Reverse oblique with a medial fragment.

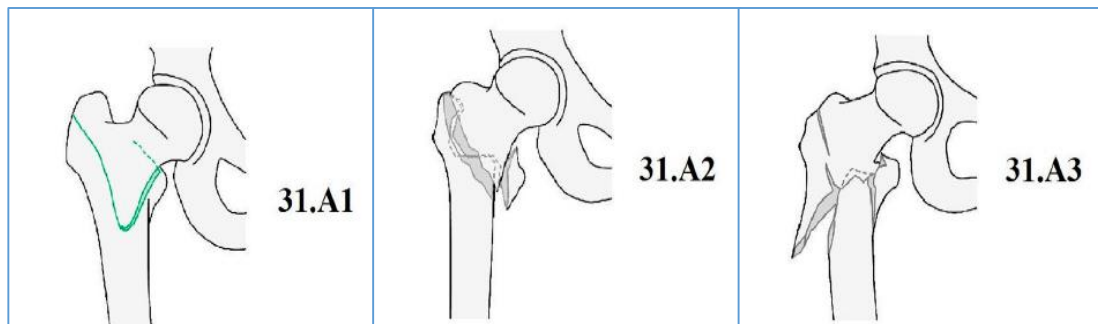


Figure 1: The old version of AO/OTA classification of proximal femur type A fractures [Image adapted from Barton et al. 2010 (54)].

The updated 2018 AO/OTA fracture classification version is also described below (Figure 2). For the purposes of this manuscript, the old version of AO/OTA classification has been used. The updated version is described below, and it is presented only for easy comparison.

Type A proximal femoral fractures are divided in the following groups:

- **Group 1 – Lateral wall intact:**
 - 31A1.1: Simple isolated fracture of the greater or lesser trochanter.
 - 31A1.2: Simple 2-part fracture.
 - 31A1.3: Any fracture with lateral wall intact (>20.5mm).

- Group 2 – Lateral wall incompetent:
 - 31A2.1: Not applicable/ no fracture type.
 - 31A2.2: Multifragmentary pertrochanteric fracture with incompetent lateral wall ($\leq 20.5\text{mm}$) and a single intermediate fragment.
 - 31A2.3: Multifragmentary pertrochanteric fracture with incompetent lateral wall and with two or more intermediate fragments.

- Group 3 – Reverse obliquity intertrochanteric fracture:
 - 31A3.1: Simple reverse oblique fracture.
 - 31A3.2: Simple transverse fracture.
 - 31A3.3: Wedge or multifragmentary fracture.

According to the 2018 AO/OTA compendium, “the lateral wall height or thickness is defined as the distance in millimetres (mm) from a reference point 3 cm below the innominate tubercle of the greater trochanter angled 135° upward to the fracture line on the anteroposterior x-ray” (52) with the foot in neutral rotation on the traction table. If the distance is $\leq 20.5\text{mm}$, the fracture is classified as A2.

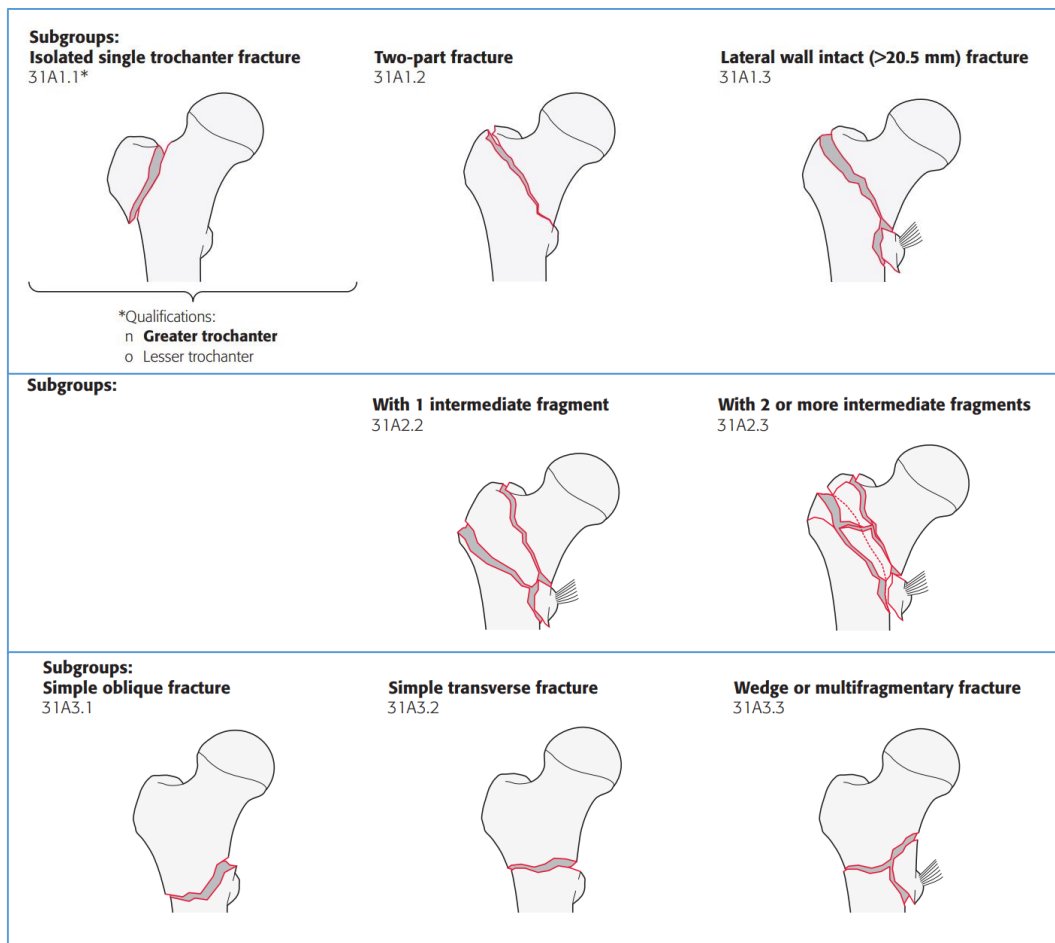


Figure 2: The updated AO/OTA classification of proximal femur type A fractures [Images adapted from Meinberg et al. 2018 (52)].

1.6.3 Reliability and reproducibility of AO/OTA classification system

Although the AO/OTA classification is one of the most complete and systematic fracture classification systems in literature, it has been criticised for its reliability and its reproducibility. The AO/OTA classification has better interobserver and intraobserver agreement for proximal femur fractures than other fracture classification systems (55); however, this applies only for the type and the group classifications. Further classification into subgroups is not reliable and it should not be encouraged (56,57). Moreover, the poor intraobserver agreement has been shown not to be dependent of surgeon's experience (57). Overall, the AO/OTA classification is a good and reliable classification system only when it is used without its group and subgroups descriptions.

1.6.4 Other classification systems of proximal femoral fractures involving the trochanteric area

1. Evans classification (1949) (58)

This classification system describes mainly the stability of the fracture. There are two types; in type I fractures, the fracture line extends upwards and outwards, from the lesser trochanter towards the greater trochanter. In type II fractures, the fracture line extends downwards and outwards, from the lesser trochanter towards the lateral cortex of the femur (reverse oblique).

Type I fractures are further subdivided in five subtypes:

- Type Ia: Undisplaced stable two-part fracture.
- Type Ib: Displaced stable two-part fracture.
- Type Ic: Three-part unstable fracture without posterolateral support due to fractured greater trochanter.
- Type Id: Three-part unstable comminuted fracture without medial support after reduction due to fractured lesser trochanter.
- Type Ie: Four-part fracture without posterolateral and medial support due to displaced greater and lesser trochanter.

Evans classification was further modified by Jensen and Michaelson in 1975 (59). According to this modification, fractures are divided in stable and unstable. Stable pattern fractures include two subtypes: undisplaced 2-part fractures and displaced two-part fractures. Unstable pattern fractures include 3-part fractures without posteromedial support due to fractured greater trochanter, 3-part fractures without medial support, due to fractured lesser trochanter and, finally, 4-part fractures. Essentially, this modified classification does not include reverse oblique fractures in which the fracture line runs downwards and outwards.

2. Kyle's classification (1979) (60)

This fracture classification mainly describes the comminution and subsequently the stability of the fracture. There are four types:

- Type I: fractures with minimum displacement and no comminution.
- Type II: displaced fractures with minimal comminution - stable pattern fractures following reduction.
- Type III: displaced fractures with large posteromedial comminution – unstable pattern fractures

- Type IV: displaced fractures with large posteromedial comminution and subtrochanteric extension.

All the above classification systems mainly describe the fractures based on the number of fragments, displacement and comminution. Out of the three systems, Evans classification is the most commonly used. However, Evans classification and its modification by Jensen and Michaelson have moderate inter- and intra-observer reliability and as a result they are not considered reliable systems for use in clinical studies (55,61).

Chapter 2

Pertrochanteric fractures: issues and challenges

2.1 Challenges in patients with hip fractures in general

Treating patients with hip fractures is very challenging. Approximately 65,000 hip fractures are being treated in the UK annually (11). As a result, surgery for hip fractures is the most common urgent procedure performed in the NHS. More than 4,000 beds are occupied by hip fracture patients every day. Inevitably, the cost of hip fractures is very high and it is around £2 billion in the UK (9). For all the above reasons, hip fractures are very common and very costly for any healthcare system.

Not only hip fractures are very common, but patients with hip fractures have multiple comorbidities (62). At least 59% of the patients will have at least one comorbidity (63). The three most common comorbidities include cognitive impairment, peptic ulcer disease and peripheral vascular disease (62). Pre-existing diseases not only increase the risk for postoperative complications and mortality (63) but cause delays in surgery. Optimising patients with hip fractures before surgery is challenging. Patients with hip fracture may not be ready for surgery due to multiple reasons including coagulopathies secondary to anticoagulant therapies, abnormal electrolytes, concomitant chest infection or need for further investigations such as echocardiography. Since early surgery is associated with reduced mortality and perioperative complications (64), it is essential to avoid any delays in surgery. By having protocols in place on how to optimise hip patients preoperatively ensures early surgery and subsequently better survival and lower complication rates.

Lastly, patients with hip fractures have lengthy hospital stay. In the 2019 National Hip Fracture Database (NHFD) report, the mean acute hospital length of stay was 15.1 days and the mean trust length of stay was 19.5 days. There is evidence that the longer the hospital stay, the higher the mortality rate (65). Not only this, but longer hospital stay inevitably will increase the total cost of care. As a result, it is important that hospital stay remains as short as possible. Several factors have been identified that may affect the length of hospital stay, such as AMTS, ASA score and pre-injury mobility status (66). However, all these factors are patient-dependent and therefore they cannot be altered. Moreover, despite all the advancements and improvements in the management of patients with hip fractures, the length of hospital stay has remained stable between 2012 - 2019 in the UK (<https://www.nhfd.co.uk/20/nhfdcharts.nsf/vwcharts/Lengthofstay?opendocument>). According to the national guidelines (9), medical care and

rehabilitation of patients with hip fractures is provided by a multidisciplinary team including orthopaedic surgeons, orthogeriatricians, nurses, physiotherapists and occupational therapists. The aim is to optimise patients for prompt surgery, to identify and manage early any potential medical complications, to mobilise as early as possible and to ensure safe discharge to their pre-hospital place of residence when possible. Overall, it has been challenging to reduce the LOS of patients with hip fractures; a lower LOS would possibly be associated with lower mortality, less complications, lower number of hospital beds occupied by hip fracture patients and subsequently lower costs.

2.2 Clinical outcomes following surgical treatment of hip fractures

Over 90% of patients with hip fractures are aged over 65 years old and have pre-existing comorbidities (67). As a result, treatment of patients with hip fractures is associated with high mortality and morbidity (7,9). Particularly, one in five patients will develop at least one complication postoperatively (63,68). Complications can be divided as medical or surgery related complications (Table 1).

Medical complications

The most commonly occurring medical complications include chest infection (6-9%) (63,69), urinary tract infection (5%) (69), and cardiac failure (5%) (63). Other medical complications include deep vein thrombosis/pulmonary embolism (1-2%) (63,68,69), gastrointestinal haemorrhage (1-2%) (63,68), myocardial infarction and stroke (1%) (63,69).

Surgical complications

Surgical complications are rarer than medical complications. From those, the most commonly encountered in clinical practice include wound infection (3%), revision surgery (0.9%), failure of fixation (0.6%), dislocation (0.5%) and periprosthetic fractures (0.3%) (69). Particularly for intracapsular fractures treated with internal fixation, the risk of non-union is 10-45% and the risk of avascular necrosis is 9-18% (67).

Table 1: Medical and surgical complications in patients with hip fractures

| Medical Complications | % | Surgical Complications | % |
|------------------------------|----------|-------------------------------|----------|
| Chest infections | 6-9% | Wound infection | 3% |
| Urinary tract infections | 5% | Revision surgery | 0.9% |
| Cardiac failure | 5% | Failure of fixation | 0.6% |
| Thromboembolic event | 1-2% | Dislocation | 0.5% |
| Gastrointestinal haemorrhage | 1-2% | Periprosthetic fractures | 0.3% |
| Myocardial infraction | 1% | Non-union (for IC) | 10-45% |
| Stroke | 1% | Avascular necrosis (for IC) | 9-18% |

IC=: intracapsular fractures

2.3 Surgical complications in patients with intertrochanteric fractures (Table 2)

Up to a third of patients with intertrochanteric fractures will develop a postoperative complication (70). Surgical complications (Figure 3) include femoral head screw cut-out (3.5%), fracture non-union (2.4%), femoral shaft fractures (1.2%) and wound infection (3.4%) (18). The overall risk of re-operation for any cause is 5.5% (18).

It is important to note that big meta-analysis reports have included studies which used the first generation of Gamma nails which were associated with higher risk of femoral shaft fractures (18,67,71). Newer designs of Gamma nail have lower rates of femoral fractures (72) and therefore caution is required when interpreting these results.

Table 2: Surgical complications in patients with intertrochanteric fractures

| Complications | Percentage of patients |
|--------------------------|------------------------|
| Screw cut-out | 3.5% |
| Wound infection | 3.4% |
| Non-union | 2.4% |
| Femoral shaft fracture | 1.2% |
| Re-operation | 5.5% |
| Intra-operative fracture | 2.2% |

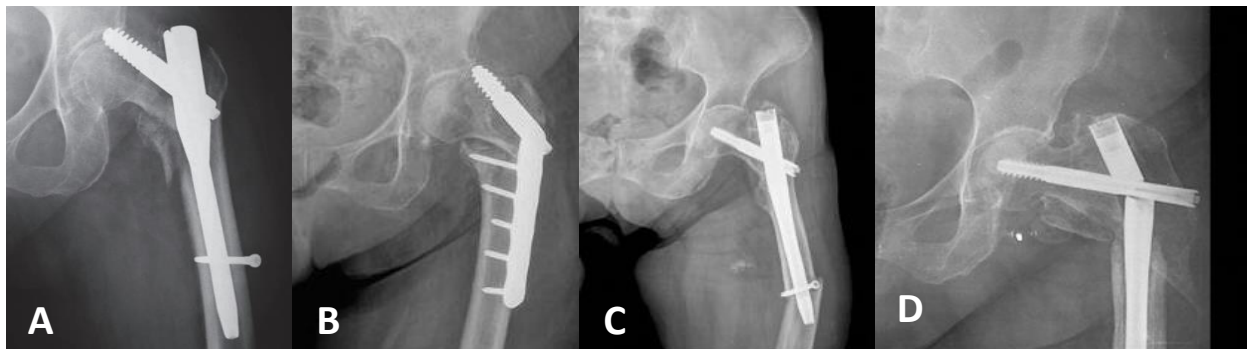


Figure 3: Metalwork complications following fixation of intertrochanteric fractures: A: Nail cut-out, image adapted from Valentini et al. 2014 (73) , B: DHS cut-out, image adapted from Boukebous et al. 2018 (74), C: Peri-implant fracture following IM nailing, image adapted from Carpintero et al. 2014 (67), D: Metalwork failure following IM nailing , image adapted by Carpintero et al. 2014 (67).

Chapter 3

Implants for stabilisation of pertrochanteric fractures: Nail vs DHS

Traditionally the gold standard treatment of pertrochanteric fractures is the dynamic hip screw (DHS), also known as the sliding hip screw (SHS) (75). This is an extramedullary device that consists of a lag screw and a plate. The screw is inserted in the centre of the femoral head and can slide within a barrel which is part of the plate. As a result, this construct allows collapse of the fracture on the axis of the screw. The plate is held on the femur with 3-4 screws, and it works as a buttress allowing progressive and controlled fracture collapse.

An alternative device to DHS is the cephalomedullary nail. As its name suggests, this is a device in the shape of a pin which is inserted in the intramedullary canal of the femur. The nail may be short or long; the former stops proximal to the isthmus of the femur while the later spans the whole femur. The nail is further stabilised within the femur by one or two cephalic screws proximally and one or two locking screws distally. The length of the nail and the number of the cephalic and distal locking screws are factors that affect the overall stability of the construct.

3.1 Technical features of nails

Length of nail

Both short and long nails have been used for the fixation of pertrochanteric fractures. Several studies have assessed whether the length of the nail affects surgical outcomes (75–78). There is good evidence to suggest that short nails are associated with shorter operative time and less blood loss when compared to long nails (77,78). Long nails require the use of fluoroscopy for the insertion of the distal locking screws and this increases the overall operative time while short nails do not require fluoroscopy as the screws are inserted through a jig. Moreover, long nails require reaming of the medullary canal so that the nail will pass through the narrow isthmus and this results to increased blood loss (77,79–81). On the other hand, short nails do not require any reaming and thus the blood loss is lower.

With regard to the risk of femoral shaft fractures at the level of the tip of the nail, early designs of short nails were associated with high risk of peri-implant fractures (82,83). However, following changes in the design of the nail, including a shorter length (180mm), a lesser mediolateral curvature of 4° and a taper

design with a proximal diameter of 17mm and distal diameter of 11mm, the risk of peri-implant fractures decreased from 18% (82) to 2% (78). However, new evidence from the most recent Cochrane review showed that newer design nails have comparable to older design nails risk of peri-implant fracture (84). Moreover, a randomised control study (RCT) and several retrospective comparative studies comparing long and short nails have found no significant difference in the risk of femoral shaft fracture or cut-out (78,82,85,86). Consequently, the newer designs of short nails have similar risk for peri-implant fractures as the longer nails.

Number of cephalic screws

Another area of variability in the design of intramedullary nails is the number and the configuration of the screws in the femoral head. Several biomechanical studies have compared one and two screw configurations. Studies on cadavers have shown that a two-screw configuration is stiffer, controls rotational movements in the femoral head better, and prevents varus collapse better than a single screw (87,88). Furthermore, the use of two screws is recommended for younger and more active patients with sound bone quality whereas this configuration should be avoided in elderly patients with osteoporotic bone and thus high risk of cut-out (89).

With regard to the size of the two screws, several combinations have been tested; two small screws or two different size screws. All combinations have been compared to a single screw and all had similar results. There hasn't been any direct comparison between two different dual screw configurations yet (89,90).

Despite the plethora of biomechanical studies on cadavers, there is paucity of clinical studies comparing one and two screws. An RCT has showed that sliding of the screws and shortening of the femoral neck is less when two screws were used (91). However, this study showed that there was no difference in the functional outcomes between the two groups and therefore it was concluded that shortening of the neck does not affect functional outcomes. Similarly, in another study, a two-screw configuration was associated with less leg shortening and less varus collapse than a single-screw configuration (no functional outcomes were reported in this study) (92).

Overall, there is a consensus that the two screw configuration results in stiffer constructs; however, it is arguable whether this is desirable in patients with osteoporosis or whether this reduces the risk of cut-out or whether this improves functional outcomes.

Distal locking

A nail can be distally locked with screws or not. Distal locking increases the rotational stability and subsequently the overall fracture stability. Secondly, it prevents fracture collapse and thus limb shortening. Thirdly it enhances early mobilisation.

Biomechanical studies on cadavers have shown that distal locking increases the overall stiffness of the construct (93,94). However, unlocked nails can also tolerate similar or even higher torsional loads before they fail. Moreover, distal locking may be unnecessary in stable intertrochanteric fractures with good cortical contact at the fracture site (93,94). In clinical practice, two RCTs have showed that there is no difference between locked and unlocked nails in terms of complications, union rates and functional outcomes in stable intertrochanteric fracture (AO/OTA 31- A1 and A2) (95,96). Both studies have confirmed the benefits of avoiding distal locking which include reduced surgical and fluoroscopy time, less blood loss and less residual thigh pain.

Overall, it can be said that stable pertrochanteric fractures do not require distal locking screws; however, distal locking is recommended for severely comminuted or unstable fracture patterns (e.g. reverse oblique intertrochanteric and subtrochanteric fractures) when there is limited cortical contact at the fracture site (75).

Surgical technique

The surgical approach for intramedullary nailing and extramedullary plating differs significantly. The insertion of a nail is done mostly percutaneously (i.e. minimal invasive technique) through a small wound proximal to the greater trochanter. The proximal and distal locking screws are inserted through two further stab incisions. This approach does not cause any significant damage to any of the muscles around the hip. Whereas, for the application of a DHS plate on the lateral border of the femur, a big dissection is required in order to lift off the bone a big portion of the vastus lateralis. As a result, surgery for intramedullary nailing causes less surgical trauma and subsequently someone would expect the risks of bleeding and surgical related complications to be lower.

3.2 Biomechanical comparison between intramedullary and extramedullary implants

Intramedullary fixation is considered biomechanically advantageous to extramedullary plate fixation. This is mainly because the distance between the implant and the femoral head is longer with extramedullary fixation and consequently the moment arm is expected to be bigger at the tip of the screw which will subsequently result in higher forces and, theoretically, this would increase the risk of cut-out (97,98).

Moreover, cadaveric studies have showed that nail constructs are more rigid than DHS constructs (rigidity is a material's resistance to bending) (99,100). This is because of the big size of the intramedullary rod that acts a buttress to fracture collapse and at the same time it does not allow medial displacement of the femoral shaft.

Finally, nail constructs with two cephalic screws are biomechanically stronger than implants with a single cephalic screw (strength is a material's resistance to breakage) (87,88). Since the DHS consists of only one screw in the femoral head, it will be less rotationally stable than a nail with two cephalic screws and as a result it will be less biomechanically strong.

3.3 DHS vs cephalomedullary nail for pertrochanteric fractures

Despite the abundance of studies, there is still no clear evidence whether intramedullary nails are better than extramedullary devices for the treatment of pertrochanteric type A2 fractures. It seems that practices differ in different health care systems. For instance, in the UK 77.9% of intertrochanteric A1 and A2 fractures were fixed with a DHS in 2019 (11) while in the USA only 19% of the surgeons would use this device (101). The big difference in practice in these two healthcare systems is most likely mainly due to the different sources of funding; a publicly funded healthcare system such as the NHS has limited resources and practice is usually determined by the cost-effectiveness of the available treatments. Whereas, in a private healthcare system, like in the USA, more expensive treatments can be afforded as long as the overall service remains profitable for the healthcare provider. Although intramedullary nails are the most commonly used fixation devices for these fractures worldwide, there is little evidence to justify this. Cadaveric studies have showed that intramedullary devices are biomechanically superior to extramedullary devices but clinical studies have failed to reveal any superiority of one device over the other (101). There is, however, good evidence to support the use of a specific device for specific type of fractures. For stable 2-part intertrochanteric fractures (AO/OTA 31-A1) DHS is considered the most cost-effective implant with no inferior complications and functional outcomes compared to intramedullary nails (102–105). Whereas for highly unstable subtrochanteric type fractures (AO/OTA 31-A3) intramedullary devices have lower failure rates than extramedullary devices and therefore intramedullary fixation is recommended for this type for fractures (106). However, there is no consensus as to the best implant to use for fractures with questionable stability (AO/OTA 31-A2).

The most recent Cochrane review, which was published in January 2022, found that extramedullary and intramedullary devices have similar outcomes, including functional outcomes, mortality, delirium and unplanned return to theatres, with regard to surgical fixation of intertrochanteric fractures (84). However,

there is significant difference in the profile of adverse events between the two fixation methods; extramedullary devices are associated with higher risk of superficial wound infections and higher risk of non-unions whereas intramedullary devices are associated with higher risk of intraoperative and later implant-related fractures. More interestingly, this review found that the risk of later peri-implant fractures has not changed significantly following changes in the design of cephalomedullary nails; subgroup analysis revealed no difference in the risk of peri-implant fractures between studies published before and after 2010. Similar to the findings of previous meta-analysis (18), the 2022 Cochrane review (84) also concluded that health-related quality of life outcomes are under-reported in the majority of the studies (18). Moreover, the reviewers recommend for future studies to focus on unstable fracture patterns and studies should aim to identify differences in health-related quality of life.

With regard to functional outcomes, only a small number of the current RCTs have reported such outcomes and comparisons are very limited (18). For instance, in the meta-analysis of Yun et al. out of the 43 included RCTs there were only 10 comparisons, using 6 different outcome scores. Similarly, in the meta-analysis of Wessels et al. (which included 12 studies and 10,402 patients) no comparisons were feasible due to the lack of comparable measures across the studies (27).

With regard to the current evidence from individual studies, there are mixed results: a number of studies have found that nail fixation leads to better functional outcomes (107–111) whereas other studies have found that there is no difference between the two implants (22,23,54,112–114). A summary of the studies and the reported functional outcomes is shown in Table 3. Overall, current literature is inconclusive with regard which implant is associated with better functional mobility.

Table 3. Reported functional outcomes in RCTs on intertrochanteric fractures

| | Treatments compared | Functional outcomes | Outcome (nail vs DHS) |
|-----------------------------|-------------------------------|---|----------------------------------|
| Yu et al. 2016 | PFNA vs DHS | HHS | Nail > DHS |
| Sanders et al. 2016 | InterTAN vs SHS | FIM, LEM, TUG , 2MWT | Nail = DHS |
| Reindl et al. 2015 | InterTAN/ TFN/Gamma vs DHS | LEM, 2MWT, TUG, FIM | Nail = DHS |
| Zehir et al. 2015 | PFNA vs DHS | Unrestricted walking | Nail > DHS |
| Aktselis et al. 2014 | Gamma vs AMBI SHS | Barthel index, EQ-5D Parker Mobility score | Nail > DHS Nail = DHS |
| Matre et al. 2013 | InterTAN vs SHS | TUG, EQ-5D, HHS | Nail = DHS |
| Parker et al. 2012 | Targon vs SHS | Parker Mobility score | Nail > DHS |
| Barton et al. 2010 | Gamma vs SHS | EQ-5D, Change in mobility | Nail = DHS |
| Xu et al. 2010 | PFNA vs DHS | Mobility score | Nail > DHS |
| Utrilla et al. 2005 | Gamma vs SHS | Mobility score | Nail = DHS |
| Saudan et al. 2002 | PFN vs DHS | Mobility score | Nail = DHS |

3.4 Nail vs DHS: Current evidence on type A2 unstable pertrochanteric fractures

A recent meta-analysis by Zhu et al. has reported outcomes from 6 RCTs which compared fixation of specifically AO/OTA 31-A2 fractures between intramedullary nail and SHS (19). This study included 909 patients in total. Overall, it was concluded that fixation with intramedullary nail is superior to fixation with SHS.

Operative details:

The meta-analysis found significant difference in the intraoperative blood loss between the nail and SHS groups. Two studies were included in the analysis and blood loss was found to be on average 204mls lower in the nail group (19).

With regard to the length of surgery and the number of patients who required blood transfusion, there was no significant statistical difference between the nail and the SHS groups; however, sensitivity analysis showed that there was insufficient evidence to verify these results.

Lastly, radiographic screening time was found to be very similar between the groups (4 studies included in the analysis). Sensitivity analysis showed that these results were reliable.

Fracture fixation complications:

Overall, there was no difference between the groups in fracture fixation complications. More precisely, there was reliable evidence that there is no difference between the groups with regard to intraoperative or later fractures of the femur, cut-out, reoperations, and other fracture related complications (i.e. haematoma, medialisation, loss of reduction, fixation failure, and screw migration). In this cohort of patients, the prevalence of cut out was 2.8% in the nail and 3% for the SHS group., the prevalence of femoral shaft fracture was 1.1% in the nail and 0.5% in the SHS group, the prevalence of intraoperative fracture was 2.7% in the nail and 1.3% in the SHS and the prevalence of reoperation was 1.6% in the nail and 2.1 % in the SHS group.

Although statistical analysis showed that there was higher risk of superficial or deep infection in the SHS group, sensitivity analysis did not confirm the results and therefore it was concluded that there is insufficient evidence. More specifically, the prevalence of wound infection was 2% in the nail and 5% in the SHS group.

Postoperative complications:

There was reliable evidence that there was no difference between the groups in postoperative complications including pressure sores, pneumonia, thromboembolic complications, and other medical complications (such as cardiovascular, neurologic complications, delay in wound healing and urinary tract infection).

Length of stay was reported in 4 studies (54,108,109,111). There was insufficient evidence whether the difference in the groups was statistically significant.

Leg shortening:

Two studies reported outcomes on leg length. Only in the study of Zehir et al. the technique of measuring neck shortening was described (108); according to this technique described by Zlowodzki et al., an outline of the contralateral hip was outlined and this was compared to the outline of the injured hip (115). The vertical distance between the two outlines represents the femoral neck shortening.

Statistical analysis from the data from the two studies showed that leg shortening was significantly less by a mean of 2.73mm in the nail group than in the SHS group. Both studies reported very similar results: femoral shortening was on average 2.63mm in the nail (PFNA) group and 5.53mm in the SHS in the study of Zehir et al. and 2.6mm in the nail (PFNA) and 4.8mm in the SHS in the study of Xu et al.

Interestingly, Zehir et al. found that more patients treated with a nail were able to mobilise independently at 6 months. Moreover, less patients treated with a nail had moderate degree (5-10mm) of femoral shortening. However, femoral shortening did not correlate with the number of patients who achieved walking recovery or independent walking. Therefore, they concluded that independent walking was attributable to patient-related factors rather than better anatomical restoration.

Overall, the results of this meta-analysis suggest that although there was a statistically significant difference in leg shortening between the groups, this difference was not clinically important.

Other outcome measures:

Parker mobility score was reported in 2 RCTs (109,111). Statistical analysis showed that there was good evidence that Parker score at 3 and 12 months was significantly higher in the nail group than in the SHS group.

Four studies reported 1-year mortality rates (23,54,109,111). The mortality rate at 1-year was 16.8% in the nail group and 12.8% in the SHS group and this was not a statistically significant difference.

Two studies reported data in days to mobilisation with walking aids (111,116). Meta-analysis of the two studies showed that patients in the nail group mobilised with aids statistically significantly in less days than patients in the SHS group.

Final conclusions:

Overall, this meta-analysis showed that there is no difference between intramedullary nailing and extramedullary fixation with regards to adverse events (i.e. fracture fixation and postoperative complications). However, the results suggest that intramedullary nailing is superior to extramedullary fixation of unstable fractures with regard to intraoperative blood loss and functional mobility (i.e. Parker score, days to mobilise with walking aids).

Interestingly, lower blood loss in the nail group was not translated into lower blood transfusion rates. The average blood loss difference between the groups was 204ml. It can be argued whether blood loss of 204ml was clinically significant since it did not lead to higher rates of transfusion requirements.

Moreover, meta-analysis of functional mobility outcomes (i.e. Parker mobility score and days to mobilise with walking aids) was grounded only on two studies. Before any generalisation of these results, confirmation from bigger meta-analysis would be useful.

The limitations of this meta-analysis include the small number of RCTs included, the small number of participants, the small number of studies analysed for several outcomes and the high risk of performance and detection bias of all included RCTs.

Chapter 4

Endovis proximal femoral nail: implant characteristics

4.1 Technical characteristics of Endovis EBA² nail

The EBA² is an intramedullary device recommended for the fixation of intertrochanteric fractures. It is produced by Citieffe, an Italian company which specializes in developing trauma and orthopaedics devices. It is a commonly used intramedullary nail used in Italy and it has already been used in several studies in the literature (116–120).

4.1.1 Indications

The EBA² nail comes in three versions: as a standard nail, as a medium nail and as a long nail.

The standard nail is 180mm long and the medium nail is 240mm long. These two versions are indicated for any type of pertrochanteric fracture extending up to 1cm distally to the lesser trochanter. According to the manufacturer, the EBA² standard nail is suitable for AO/OTA 31 -A1, -A2 and A3 fractures.

The long EBA² nail comes in several lengths (from 300mm to 460mm long) and it is indicated for intertrochanteric fractures that extend into the femoral diaphysis. Further indications include subtrochanteric fractures, pathological fractures, bifocal fractures, non-unions and mal-unions (121).

4.1.2 Design characteristics

The proximal diameter of the nail is 13.5mm and the distal diameter is 10mm. The proximal end of the nail is flattened laterally. In an attempt to reduce any stress risers distally, the tip of the standard and medium nails is slotted whereas the tip of the long nail is chamfer shaped. The metaphyseal angle of the nail is 5° and the neck shaft angle is 130°.

It has two femoral head locking screws in order to increase rotational stability of the construct. Both screws are allowed to collapse in a control manner. There is no option for statically locking the proximal screws into the nail. The cephalic screws are partially threaded. The diameter of the screws is 7.5mm. The manufacturer recommends the two screws to have 10mm difference in their length, with the distal screw to be the longer one.

The two shorter versions of the nail have distally one locking screw which can be inserted either in dynamic or in static fashion (dynamic fashion allows the nail to sink into the medullary canal). According to the manufacturer, distal locking is not required for stable fractures. The diameter of the screw is 5mm and the length of the screw comes in intervals of 5mm (range 30-45mm). The long nail has a hole and a slot so that to be locked with two screws distally (the screw in the slot can be used in static or dynamic fashion).

The two shorter versions of the nail do not require intramedullary reaming as they are undersized for this reason. This is aimed to result in low blood loss. Furthermore, the proximal part of the nail is flattened laterally to allow easy insertion.

Finally, the instrument set consists of only 11 instruments and the surgical technique requires only 7 steps. It is a simple kit to use, and implantation of the nail can be considered fast.

With regard to the operative technique, insertion of the nail is minimally invasive. A small incision proximally to the hip is required from where the nail is inserted. All the screws can be inserted percutaneously through stab incisions. Following the procedure, the patient will normally have 3 incisions.

Table 4: EBA² nail summary characteristics.

- Neck-shaft angle 130°.
- Metaphyseal angle 5°.
- Nail length:
 - Standard nail is 180mm and medium nail is 240mm.
 - Long nail: from to 300mm to 460mm long.
- Nail diameter 10mm – for the long nail, there are the following options: 9mm (solid), 11mm, 12mm, 13mm.
- Long nail has a curvature of 1.4 for ≤ 380 mm nails and 2.3m for ≥ 400 mm nails.
- Proximal end diameter 13.5mm for standard nail and 15mm for long nail.
- Two proximal cephalic screws; both screws have the same size (7.5mm thread diameter), the proximal screw is recommended to be 10mm shorter than the distal cephalic screw, both screws are allowed to slide into the nail.
- Distal locking screw can be inserted in static or dynamic fashion.

Nail innovations:

- Undersized implant that does not require reaming of the intramedullary cavity and thus reduced risk of blood loss.
- The proximal part of the nail is flattened laterally for easier insertion.
- The tip of the nail is slotted to minimise the risk of stress risers and thus the risk of femoral shaft fractures.
- Instrument set consist of 11 tools and standard nail can be inserted in 7 surgical steps.

4.2 Dynamic hip screw/Sliding hip screw

There are many Dynamic Hip Screw (DHS) devices in the market. For the purposes of this study, the Zimmer-Biomet Versa-Fx® fixation system was used and this system is described below.

Indications

The DHS is the gold standard treatment for intertrochanteric stable fractures (AO/OTA 31A1) (75). Other indications include intracapsular undisplaced fractures, osteotomies, and arthrodesis.

Technical features

The DHS consists of a plate and a hip screw (known as 'lag screw').

The plate is made of stainless steel and it comes in different sizes. The plate ends at its proximal end with a barrel. The barrel can be standard (38mm) or short (25mm) depending on the size of the hip screw that will be used. The barrel angle can vary from 130° to 160° but the most commonly used is 135°. The purpose of the barrel is to allow the hip screw to slide within the barrel in a controlled manner. The plate is held onto the femur with cortical screws.

The sliding hip screw is a partially threaded screw. It is also known as 'lag screw'. Its thread diameter is 13.5mm and its core diameter is 8mm. Insertion of the hip screw is aimed to be in the centre of the femoral head in the AP and lateral view on the x-rays. A tip apex distance less than 25mm has been shown to reduce the risk of cut out significantly (122). Compression at the fracture site can be achieved by using a compression screw.

For the insertions of the DHS one incision is required. It requires an open approach (in comparison to percutaneous approach for the nail) and dissection is through the vastus lateralis.

Chapter 5

Proposed line of investigation and ethical approval

5.1 Study rationale

Due to the high number of patients with a hip fracture annually, the high mortality following hip fractures and the associated economic burden, proximal femur fractures continue to be a major healthcare problem and an area of ongoing research.

According to the current literature, patients with cognitive impairment are systematically excluded or ignored in current randomised trials on hip fractures (17). The same can also be claimed specifically for studies on intertrochanteric fractures; the meta-analysis by Yu et al. included 43 randomised trials on intertrochanteric fractures and less than a quarter of them included patients with cognitive impairment (18). Moreover, none of those trials reported specific results for patients with cognitive impairment. Consequently, the results of the current trials apply to patients without cognitive impairment, and it is extrapolated that the same results may apply to the patients with cognitive impairment. Therefore, more studies that report outcomes exclusively for patients with cognitive impairment are required so that better evidence becomes available for this subgroup of patients.

Moreover, there is paucity of feasibility studies assessing participation of patients with dementia in surgical interventional trials in patients with intertrochanteric hip fractures. According to the CONSORT statement, feasibility studies aim to assess whether future definitive studies can be done, should be done and how can be done (123). They are conducted in a smaller scale than definitive trials and they differ from definite trials in terms that their purpose is to assess feasibility rather than effectiveness or efficacy. As a result, potential outcomes of a feasibility study include whether eligible patients can be screened, can be recruited and can be maintained in the trial, whether the outcome measures are acceptable measures to measure efficacy of the interventions and whether the outcome measures lead to preliminary estimates of potential variables which can be used as outcome measures or can be used for the power calculation of the definitive trial (123). Due to the lack of feasibility surgical interventional studies in patients with hip fractures, it can be argued that this is one of the reasons why methodology design studies have found that inappropriate patient reported outcome measures are being used in the current trials (21,26). As a result, it is a common conclusion in meta-analysis studies on intertrochanteric

fractures that there is insufficient evidence on functional outcomes and no comparisons can be made (18,19,27,71,124).

Finally, there is still no consensus whether intramedullary fixation of unstable intertrochanteric AO/OTA A2 fractures is advantageous to extramedullary fixation. There is good evidence to suggest that type A1 fractures are best to be treated with extramedullary fixation as this is the most cost-effective implant (102–105). Similarly, there is good evidence that intramedullary fixation is the preferred option for type A3 fractures as these implants are associated with lower rates of complications and failures than extramedullary implants (106). However, current evidence is conflicting for type A2 fractures (23,54,108–111,125).

5.2 Aims and objectives

For all the above reasons, a feasibility study that would assess if it possible to include patients with cognitive impairment in a randomised trial and how this can be done was deemed necessary. Therefore, the aims of this study were to:

1. Report outcomes specifically for the subgroup of patients with cognitive impairment.
2. Assess what proportion of patients with cognitive impairment can be recruited, retained and complete trials assessments outcomes at each stage of the trial.
3. Assess whether a physical assessment tool is a good test to assess functional mobility in this type of study.
4. Compare clinical outcomes between fixation with intramedullary fixation and extramedullary fixation.

The Endovis BA² nail was chosen to be used as the intramedullary implant following an agreement with Citieffe® (Bologna, Italy) who provided an educational grant that would cover the costs of the trial. The DHS (Zimmer - Biomet) was used as the extramedullary implant, as this is the implant that is routinely used in Leeds General Infirmary for the fixation of intertrochanteric fractures.

In particular, the objectives of the study were:

Primary objectives:

1. To assess the rate of patients recruited, retained and completed the study.
2. To use the 'Time Up and Go' (TUG) test as the primary outcome to assess functional mobility in patients with unstable pertrochanteric hip fractures. A physical assessment measure was chosen to remove any confounding factors associated with PROMs. It was hypothesized that patients with and without cognitive impairment would be able to complete the test and comparing the TUG times would be an objective method to compare patient's functional mobility.

Secondary objectives:

1. To assess intraoperative details of surgery (including operative time and blood loss).
2. To assess length of stay and time till ready for discharge.
3. To assess pain levels in the first 3 months.
4. To assess patient-reported functional mobility and health-related quality of life in the first 3 months.
5. To assess level of mobility at 3 months.
6. To assess place of residence at 3 months.
7. To assess intra- and post- operative complications and adverse events.

The time point of 3 months was chosen for mainly two reasons. Firstly, improvement in mobility in patients with hip fractures occurs by 3 months (126) and, secondly, it would be significantly quicker to complete the study with a 3 month follow-up rather than with a 12 month follow-up.

5.3 Ethical approval

The protocol of this study and all its amendments were reviewed by the Health Research Authority (Yorkshire and the Humber – Leeds West Research Ethical Committee, REC reference 15/YH/0440, IRAS project ID: 167114) (Appendix 1) and the study was approved on the 21/6/2016. The study was further approved locally by the Leeds Teaching Hospitals NHS Trust Research and Development (R&D) department. This study was registered with ClinicalTrials.gov (NCT02788994).

The study was conducted in accordance with the ethical principles that have the origins in the Declaration of Helsinki. All investigators involved in the study were up to date with Good Clinical Practice (GCP).

5.4 Source of funding

Citiefte® (Bologna, Italy) provided an educational grand for the study. The manufacturer was not involved with the study design, everyday trial activities, data acquisition and data analysis.

Chapter 6

Patients and Methods

6.1 Study description

This was a single centre, proof of concept study, assessing the feasibility of carrying out a randomised control trial comparing the fixation of unstable (AO/OTA 31A2) pertrochanteric fracture with an Endovis (EBA²) nail versus a dynamic hip screw (DHS) in patients with and without dementia.

All patients were recruited at Leeds General Infirmary (part of Leeds Teaching Hospitals NHS Trust). In total, sixty patients were randomised to either the nail group (EBA²) or the DHS group. All patients were screened for cognitive impairment on admission using the Abbreviated Mental Test Score (AMTS). The AMTS was assessed by the admitting clinician as part of the routine clerking of patients with a proximal femur fracture. Patients were considered to have cognitive impairment if AMTS was <8. A limitation of using the AMTS on admission to determine whether they had cognitive impairment was that AMTS could be affected by acute conditions (such as delirium, infection) and as a result it could change throughout the hospital stay. For this reason, it was clarified in the protocol that patients would remain in their initial AMTS group throughout the trial, even though their AMTS could change later during their hospital stay.

All patients had surgery within 36-hours according to the standard national hip practice. After surgery, patients were followed-up at 2, 4 and 12 weeks. Follow-up appointments for patients with hip fractures are not routinely planned and they were arranged specifically for research purposes. A telephone call was planned to take place at 6 months after the last follow-up visit to ensure that any late adverse events had been recorded.

At each follow-up, study specific data were collected as outlined in the Table 5.

Table 5: Summary schedule of trial assessments.

| | Baseline | 2 weeks | 4 weeks | 12 weeks | Final telephone review |
|-------------------------|----------|---------|---------|----------|------------------------|
| Pain NRS | ✓ | ✓ | ✓ | ✓ | NA |
| TUG test | NA | ✓ | ✓ | ✓ | NA |
| Lower Extremity Measure | ✓ | ✓ | ✓ | ✓ | NA |
| London Handicap scale | ✓ | ✓ | ✓ | ✓ | NA |
| DEMQOL | ✓ | ✓ | ✓ | ✓ | NA |
| Plain X-rays | ✓ | ✓ | ✓ | ✓ | NA |
| Residential status | ✓ | NA | NA | ✓ | ✓ |
| Mobility status | ✓ | NA | NA | ✓ | ✓ |
| Adverse events | ✓ | ✓ | ✓ | ✓ | ✓ |

Days till ready for discharge, LOS and intraoperative variables have not been included in this table.
NA: Not applicable

6.2 Study duration

Over a period of 5 years (2008-2013), 575 patients (on average 115 patients per year) presented with pertrochanteric hip fractures and treated with DHS in Leeds General Infirmary. Given a conservative estimate of 40% recruitment, a recruitment rate of 40 patients per year was estimated.

Therefore, a study period of 2 years was assigned; 18 months for patient recruitment, 3 months for the last patient to complete the follow-up and 3 months if any delays in recruitment.

The study opened for recruitment in July 2016 and the first patient was recruited on 28/7/2016. The last follow-up was completed on 25/1/2018. The overall recruitment and follow-up period took 18 months.

6.3. Patient selection

6.3.1 Inclusion criteria

1. Adult patients with age between 55 and 95 years.
2. Fresh unilateral unstable (AO/OTA 31A2) pertrochanteric hip fracture (fracture type was discussed and determined during the daily trauma meeting in the presence of Trauma & Orthopaedic consultants. An AO/OTA classification poster for A- type hip fractures was hanged in the room for reference at any time).
3. Surgery within 7 days.
4. Informed consent taken by patient or by a personal or nominated consultee before surgery.
5. Patient deemed able to complete the study assessments and follow-up schedule in the opinion of the research team.

6.3.2 Exclusion criteria

1. Unable to ambulate pre-injury, even with walking aids.
2. Not fit for surgery.
3. Previous stroke with residual lower limb weakness.
4. Recent myocardial infarction (up to 60 days).
5. Presence of additional fracture in the ipsilateral or contralateral leg.
6. Proximal femoral fractures other than -A2 type (i.e. AO/OTA 31- A1 or -A3).
7. Pathological fracture.
8. Poor life expectancy (patients who were treated palliative).
9. Patients with known renal or hepatic failure as defined by elevated transaminases ≥ 2.0 x upper limits of normal for serum aspartate aminotransferase or serum alanine aminotransferase, or significantly impaired renal function as determined by a derived creatinine clearance of ≤ 30 mL/min using the Modification of Diet in Renal Disease equation.

6.3.3 Withdrawal criteria

1. Withdrawal of consent by the patient or by the consultee.
2. Ineligibility or surgery different to EBA² nail or DHS.
3. Patient not compliant.
4. Significant adverse event following which patients were not able to continue in the trial (i.e. death).

Unless the patient specifically withdrew consent for their data to be stored, all data collected from them continued to be stored as per the original patient consent.

Patients who were withdrawn from the study early were not replaced.

6.4 Patient screening

Screening of patients took place daily. Usually, the patients were identified before the start of the trauma meeting. After patients were identified and deemed eligible, they were approached by the research team prior to surgery. They were given verbal information about the trial and a printed 'Patient Information Sheet' with details about the rationale, design, and personal implications. They were then given time to consider their participation with their family and/or other healthcare professionals. If the patients were keen to participate in the trial, a written consent was sought.

Following consenting, the patients were fully screened for eligibility. Successful screening was followed by online randomisation.

The patient information sheet and the consent forms used can be found in the Appendix 2 and 3 respectively.

6.5 Consent process

Patients with capacity

Patients with capacity to consent were asked to provide informed written consent. Patients could refuse consent or withdraw from the trial at any time without giving reasons and without prejudicing any further treatment. The process of obtaining written consent was clearly documented in the patient's medical notes.

Patient without capacity

For patients without capacity to consent, informed consent was obtained as set out in the guideline of "Mental Capacity Act 2005". As this was not a clinical trial of an investigational medicinal product (non-CTIMP), the person to be approached to give consent on behalf of the patient was selected according to the following hierarchy:

1. Personal consultee: This was someone who cared for the patient or was interested in his or her welfare other than in a professional capacity or was paid to do so. Reasonable steps were taken to identify such a person.

2. Nominated consultee: This was usually the named consultant primarily responsible for the patient's medical treatment and had no connection with the trial. A nominated consultee was considered when a personal consultee was not available.

If a patient would gain capacity during the hospital stay, they had to be re-consented.

6.6 Randomisation process

All patients entered screening were given an identification number, which was used throughout the trial. Patients who completed full screening successfully and gave written informed consent, were randomised into either the 'nail' group (EBA² nail) or the 'DHS' group. Randomisation was carried out using an online randomisation tool provided by the King's Clinical Trials Unit. Randomisation was by permuted blocks, stratified for cognitive status (AMTS<8 or AMTS≥8).

Six patients were randomised after a coin toss performed by staff of Kings Clinical Trial Unit. This occurred because the server at Kings Trial Unit was down, and it was impossible to randomise using the online system. The result of the coin toss was passed to the research team on the phone (to avoid any delays for surgery) and it was later confirmed by email. This deviation in the randomisation process could potentially introduce selection bias. However, this procedure was considered reasonable and appropriate by the trial statistician and by the staff at Kings Clinical Trial Unit.

Patients were stratified according to their AMTS. The AMTS was assessed by the admitting clinician during the routine initial clerking. Patients with AMTS≥8 were deemed as cognitive intact, whereas patients with AMTS<8 were deemed as cognitive impaired. No changes to patients AMTS status were made following randomisation.

6.7 Study blinding

Patients were not informed of their allocation but could not be considered blinded as they could guess which group they had been allocated to, based on the size and number of the incision. Surgeons and the research team had also to be aware of the group allocation for obvious reasons. However, the assessor of the TUG test was blinded to group allocation.

6.8 Study treatments

The implants used in this trial are shown in Figure 4.

Patients who were randomised to the 'DHS' group received a Dynamic Hip Screw (Zimmer - Biomet).

Patients who were randomised to the 'nail' group received the Endovis EBA² nail (Citieffe).

The EBA² nail and the DHS used in this trial have already been described in section 4.1 and 4.2 respectively.

For the purpose of this trial, a standard size nail and an end cap were used in all patients. All nails were locked distally in static mode. With regards to the DHS, a 4-hole plate was used unless the surgeon felt that a longer plate was required. A 135° barrel was used routinely unless the operating surgeon felt that a different angle fits patients' anatomy better.

All procedures were performed by a Consultant Orthopaedics Surgeon or by a Registrar competent to perform this procedure independently.

All surgeons involved in the trial were familiar with both fixation methods; therefore, there was no anticipated learning curve.

The follow-up assessments were carried out mainly by the author of this manuscript and a research nurse.

The TUG test was performed by a health care professional based in the fracture clinic at Leeds General Infirmary and had no connection with the trial. The health care professionals who performed the TUG test were blinded to the randomisation group.



Figure 4: Implants used in the trial; A: Endovis BA² nail (Citieffe) (121), B: Dynamic Hip screw (Zimmer-Biomet) (127)

6.9 Methods of assessment

6.9.1 Feasibility assessment variables

Feasibility assessment was based on successful recruitment, retention and completion of all follow-up visits in suitably eligible patients with and without dementia.

Recruitment:

In order to assess the feasibility of recruiting patients, the proportion of patients who were screened and participated in the study, the proportion of patients who were approached and participated the study, and the proportion of patients who were eligible and participated in the study were calculated. Reasons for declining to participate, and reasons for ineligibility, were recorded.

Retention and completion:

To assess the feasibility of retaining patients in the study, the proportion of patients who completed the week 4 visit and the proportion of patients who completed the week 12 visit were calculated. Patients were not required to give reasons for withdrawing from study participation but if a reason was given, this was recorded.

6.9.2 Efficacy assessment variables

Timed Up and Go (TUG) test

The intended efficacy assessment variable was the Timed Up and Go (TUG) test. This is a test that measures the time taken for the patient to stand up from a seated position, walk three meters, turn around, walk back to the chair and sit down. It is widely used to assess functional mobility in the elderly and frail people (38). TUG times depend on the type of the mobility aid people use and a use of a standardised mobility aid is recommended when comparing TUG times in patients with hip fractures (128). Therefore, all patients were asked to use the same 'rollator' whether they needed it or not. They were given verbal instructions how to perform it, but no demonstration was shown. They were asked to perform the test as fast as they could do so safely. Each patient was asked to perform the test three times. All times were recorded but the fastest time was used in the efficacy analysis. Also, the number of times that the patient was able to perform the test was recorded and analysed. All times were recorded by a healthcare staff who were not part of the trial, and they were not aware of the randomised treatment.

6.9.3 Intraoperative outcomes

Duration of surgery

Duration of surgery was defined as the duration of the surgical procedure, starting from 'knife to skin' to wound closure.

Intraoperative blood loss

1. Blood loss - ml of blood in the suction tube

The amount of blood collected in the suction tube was quantified at the end of the procedure. Any amount of 'wash' used during the operation was subtracted from the overall amount in the suction tube.

2. Blood loss – weight of surgical gauzes

At the end of the procedure, all surgical gauzes used and stained with blood were weighted. The weight of a dry swab multiplied by the number of gauzes used, was subtracted from the overall weight of all gauzes.

Blood transfusion requirements

The number of blood units transfused within the first week from surgery was recorded.

6.9.4 Perioperative outcomes

Length of stay (LOS)

The overall length of stay was calculated (numbers of days from date of admission till the date of discharge from the acute hospital).

Duration until ready for hospital discharge

The patient was deemed ready for discharge when they were medically fit as well as safe to discharge. The decision about when the patient was safe to discharge was made by the physiotherapy team. The number of days between surgery and 'ready for discharge' was recorded. The additional duration of hospital-stay due to non-medical reasons was not 'counted' for this assessment.

Analgesia used – morphine equivalent dose

The amount of opioid analgesia required postoperatively within the first two weeks was recorded. Any long-term (commenced prior to this injury) transdermal opioid patches were recorded but not counted towards the overall morphine equivalent dose.

6.9.5 Patient-reported outcome measures (PROMS)

Pain Numeric Rating Scale (NRS)

Pain levels were assessed using the pain numeric rating scale (NRS). This is a printed vertical 10-point scale ranging from 0 to 10 (bottom to top respectively); 0 represents 'no pain at all' and 10 represents 'the most severe pain ever' (Appendix 4). Patients were given verbal instructions and were asked to select a number on the scale that best reflects the intensity of the pain they had 'on that day'. The patients' ability to understand the scale was recorded. The method is recommended by the British Geriatrics Society, the British Pain Society and the Clinical Standards Department of the Royal College of Physicians to be used in the assessment of pain in the elderly (129). It has also been used in patients with mild to moderate cognitive impairment and it has been shown to be a valid and reliable tool.

Lower Extremity Measure (LEM)

Functional mobility was assessed using the Lower Extremity Measure (LEM) in patients with AMTS \geq 8. This is a 29-item questionnaire relating to daily activities and patients must select an answer from a scale of five levels of difficulty, ranging from 'impossible to do' to 'not at all difficult' (Appendix 5). If a patient considered an activity in the list was not applicable, this was scored as NA. After verbal instructions, the questionnaire was self-administered; help was provided if only requested by the patient and it involved only reading the questions. No explanations of the questions were given. To obtain pre-injury scores, patients were asked to recall their ability on the day prior to fracture. The method has been validated in patients with hip fracture and found to be responsive to change (37).

The London Handicap Scale (LHS)

A 2nd questionnaire was used in patients with AMTS \geq 8 to assess participation in activities of everyday living. The London Handicap Scale (LHS) is a measure of the disadvantaged experience due to ill health (49). It consists of 6 domains: mobility; physical independence; occupation; social integration; orientation; economic self-sufficiency. Each domain has 6 levels, arranged in order of increasing disadvantage from 'no disadvantage' to 'most severe disadvantage' (Appendix 6). Pre-injury scores were obtained by asking

the patients to think about their activities during the week before fracture. It has been used mainly in patients with chronic, multiple or progressive disease and it has been validated in patients following hip and knee replacement (50) but not in patients with hip fractures.

Dementia Quality of Life (DEMQOL)

Patients with AMTS<8 were administered the Dementia Quality of Life (DEMQOL) questionnaire. This is a tool to assess health related quality of life in patients with cognitive impairment (31). This tool consists of 2 questionnaires; the DEMQOL which is a 28-item interviewer administered questionnaire answered by the patient and the DEMQOL-proxy (or carer) which is a 31-item questionnaire answered by the caregiver (family member or carer) (Appendix 7 and 8). The questionnaire covers 4 domains: emotion, memory, ability to carry out daily living activities, perception of overall quality of life. All questions are answered with the same 4-point Likert scale; (1= a lot, 2= quite a bit, 3= a little, 4= not at all). The higher the overall score, the better the health-related quality of life is. Its use has been very limited in the literature and it has not been validated yet in patients with hip fractures and cognitive impairment (31,32).

6.9.6 Other assessment variables

Mobility status

Patients were assessed for their mobility status during screening and at 12 weeks. The mobility status was recorded as: 1. No use of aids, 2. Use of one stick or crutch, 3. Use of two sticks or crutches, 4. Use of a walker or frame, 5. Mobile with wheelchair only.

Place of residence

Place of residence was recorded on admission and at 12 weeks. It was recorded as: 1. Live in own house, 2. Live with family, 3. Live in residential home, 4. Live in nursing home, 5. Other (e.g. hospital).

American Society of Anaesthesiologists (ASA) classification system

The ASA score is a subjective score which is used to assess patient's health status prior to surgery. It is graded from one to six; 1. No comorbidities, 2. Mild systemic disease, 3. Severe systemic disease, 4. Severe systemic disease which is a constant threat to life, 5. A moribund patient who is not expected to live 24 hours without the operation, 6. A declared brain-dead patient who is undergoing organ retrieval. The ASA score was recorded from the anaesthetic records. The ASA score was used as an indicator of the morbidity of the patients.

Charlson comorbidity index (CCI)

Charlson comorbidity index is a tool to predict ten-year survival (130). It has 10 components; each component takes a score depending on the severity of that specific medical condition. The overall score is a predictor of 10-year survival. It has been widely used in clinical practice and research since it was first described in 1987. It was used in this study to assess the morbidity of patients in addition to the ASA score.

Comorbidities

Patient's comorbidities and all their contaminant medications were recorded.

6.9.7 Radiographic outcomes

At each follow-up visit, patients had an AP pelvis and a hip lateral plain X-ray. All radiographs were obtained in the main radiology department and the same protocol was used every time. Patients were supine with both lower limbs internally rotated 20°. Prior to any calculations done, all images were calibrated using the known dimension of the implants. All measurements were performed independently by two surgeons. When there was discrepancy between the two assessors, an opinion from a third assessor was sought.

The following radiographic outcomes were assessed:

Tip-apex distance (TAD)

The tip-apex distance is a radiological measurement described by Baumgaertner in 1995 as a predictor of failure of metalwork in pertrochanteric fractures. It is calculated as the sum of the distance between the tip of the lag screw and the apex of the femoral head in the AP and lateral view. If the TAD is less than 25mm, then the risk of failure of the fixation is very low (122). It is considered as the most important predictor of metalwork failure. The TAD was calculated from the X-rays taken at 2 weeks. For the purpose of this study, the TAD was measured from the distal proximal femoral screw similarly to other studies (22,23,54,98,108,112).

Neck-shaft angle

The neck-shaft angle was also used as a measure to assess fracture reduction during surgery. Moreover, the neck-shaft angle was used to assess varus collapse, which is the most common mode of failure of pertrochanteric fractures. It was measured as the angle between a line through the long axis of the femur and a second line coming through the middle of the neck and through the centre of the femoral head. It

was measured at each follow-up visit. To assess varus collapse, the neck-shaft angle difference between week 2 and week 12 was assessed.

Secondary collapse was assessed by the following three variables:

1. Femoral neck shortening

A common complication of pertrochanteric fractures is shortening of the femoral neck (neck collapse). This is more pronounced in unstable comminuted fractures. Although this can lead to leg length shortening and abductor muscle weakness, it is considered to an extent as a desirable event to happen as it enhances fracture stability and allows the fracture to unite. Moreover, the principle of the dynamic hip screw is to allow controlled collapse of the neck in the direction of the screw.

In this study, femoral neck shortening was measured with two different techniques:

- A. The distance between the tip of the lag screw and the barrel of the DHS plate or the nail. The difference in this distance was considered as neck collapse (Image A, of figure 5). This technique has previously been described in the literature (23).
- B. The length of a line starting from the medial apex of the femoral head and finishing at the lateral edge of the femur and running through the middle of the neck. This distance was compared to the contralateral side (Image B of figure 5). For patients who had a joint arthroplasty in the contralateral hip, this measurement was not performed. This technique has previously been described in the literature (131).

2. Medialisation

Another complication of pertrochanteric fractures is medial translation of the femoral shaft in relation to the proximal fragment. This is known as medialisation or medial displacement of the fracture. The distance between the proximal fragment of the neck and the distal fragment of the shaft was counted as medialisation. Medialisation of >5mm is considered clinically significant (112). We assessed the number of patients with >5mm medialisation but also the amount of medialisation at each time point.

3. Leg shortening

Axial leg shortening was measured on the AP pelvis X-rays. The difference in the distance of the lesser trochanter (most medial point) to the trans-ischial line between the injured and the contralateral unaffected hip was recorded as leg length shortening. This technique has been compared to other techniques measuring leg shortening and it has been found to be the most accurate (132).

Fracture union (RUSH score)

The Radiographic Union Score for Hip (RUSH) score is a tool that has been developed to assess bone healing in intertrochanteric hip fractures (133). It is a previously validated tool that has been shown to improve agreement of fracture healing between radiologists and orthopaedic surgeons (134,135). It consists of four components: cortical bridging (of anterior, posterior, medial and lateral cortex), disappearance of fracture line in the cortices (anterior, posterior, medial and lateral cortex), fracture consolidation and disappearance of the fracture line. Each item is scored 1-3. Score 1 is given if there is no evidence of healing and score 3 if there is evidence of complete bone healing. The overall RUSH score ranges from 10 to 30. A score ≥ 18 is suggestive of united fractures whereas a score < 18 is suggestive of non-united fractures (135). It has already been used in the literature to assess fracture union in intertrochanteric fractures and it is considered an objective system to evaluate union in hip fractures (136,137).

The RUSH score was assessed at 12 weeks only. It is acknowledged that at 3 months not all pertrochanteric fractures were expected to have united.

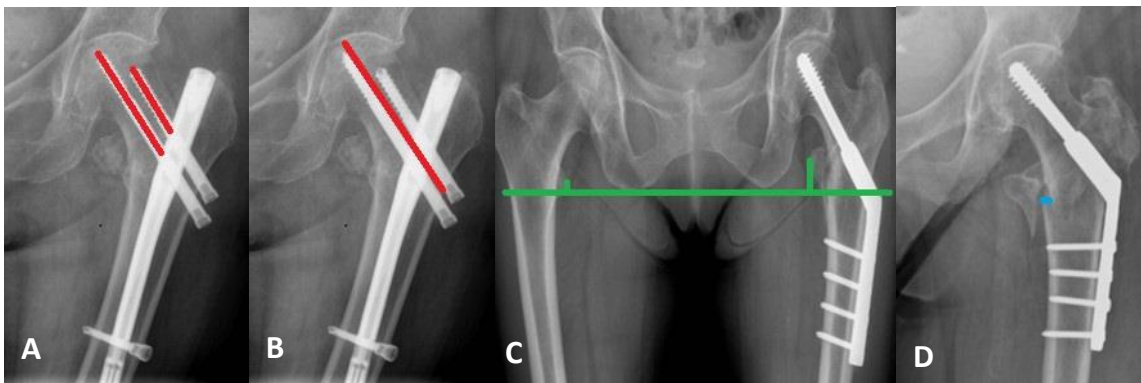


Figure 5: Radiographic outcome measurements; A: Screw collapse measured as the difference of the length of the screw (from tip till the nail or till the barrel) in two different time points, B: Neck collapse measured as the length of a line starting from the medial apex of the femoral head and finishing at the lateral cortex of the femur, bisecting the neck, C: Leg shortening measured as the distance of the lesser trochanter from the trans ischial line, D: Medialisation measured as the distance of the proximal fragment from the femoral shaft.

6.10 Complications/Adverse events

As adverse event was considered any untoward event whether it was expected or unexpected or whether it was related or not to the intervention.

As a serious adverse event (SAE) was considered any adverse event that:

1. Resulted in death.
2. Was life-threatening.
3. Required inpatient hospitalization or prolonged an existing hospital stay.
4. Resulted in persistent or significant disability.

All serious adverse events were reported to the sponsor.

6.11 Power analysis

This was a feasibility study and as such a formal power calculation was not undertaken (123,138,139). It was felt that a sample of 60 patients would be large enough to assess feasibility parameters such as the number of eligible patients, the willingness of participants to be randomised, follow up rates and response rates to questionnaires. This was based on a published study on sample size requirements for feasibility studies (138).

Moreover, the second primary objective of the study was to obtain estimates of the standard deviation of the TUG test which is needed for the calculation of the sample size in the full trial. Previously published research indicates that the mean TUG time in patients with hip fractures 4 weeks from surgery is around 30 seconds with SD=15 (41). According to a published simulation study, 30 to 50 participants per group are recommended in order to obtain accurate estimates of the standard deviation of a continuous outcome (138). According to the trial statisticians report, for this study, the probability to observe accurate estimates of SD with 60 participants was 94%, if a clinically meaningful difference in the TUG time is 6 seconds (a 20% change).

6.12 Data quality assurance

Source data verification and database reconciliation was conducted while the trial was open. More specifically a monitoring visit took place twice and assessed the quality of the data collected. All data collected in the CRFs were compared to the source data. Moreover, these visits ensured that all the trial's activities were performed according to Good Clinical Practice (GCP) standards.

Following completion of the following up visits, all data from CRFs were transferred to an excel document in preparation for statistical analysis. The whole database was verified against the original data in the CRFs to ensure there were no data discrepancies following data transfer.

As this was as small pilot study, no interim analysis was planned. According to CONSORT statement, it is uncommon for pilot studies to define criteria for early stopping (123), and therefore an interim analysis was not required.

6.13 Statistical analysis

6.13.1 Feasibility analysis

The primary outcome analysis was mainly qualitative, assessing the feasibility of recruitment and retention of eligible patients both with and without dementia. Issues presenting as barriers to recruitment or retention were analysed.

To assess the feasibility of running a full study, the following criteria were used:

- All patients attending week 4 follow-up visit should be able to perform the TUG test at least once.
- At least 90% of patients should attend the week 4 follow-up assessment.

6.13.2 Secondary outcomes

As appropriate for an unpowered proof of concept study, the primary focus of the analysis was descriptive. Descriptive summary statistics were provided for all continuous variables for each visit and for changes between visits. Frequency (absolute and relative) distributions were provided for categorical data. Separate summaries will be provided for each treatment group.

Comparisons between the groups were performed using the unpaired, two-sided t-test for normally distributed data and the Mann-Whitney U test for non-parametric data. Number of patients and percentages were compared using the Chi-square test and the Fisher exact test. Level of significance was at <0.05 . An intention to treat approach was used, apart from radiographic variables, where participants were grouped according to treatment received.

Associations between variables were explored using Pearson's product-moment correlation co-efficient to identify potential confounding factors that may require stratification against in the full trial.

Data analysis was conducted using the statistical program SPSS software (Version 23; SPSS Inc., Chicago, IL, USA).

The data analysis for this trial was supervised by Dr. Elizabeth Hensor, medical statistician, Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds.

Chapter 7:

Results

7.1 Feasibility results

7.1.1 Recruitment

Recruitment rate

Overall, 60 patients were recruited between 30.7.2016 and 14.11.2017 (within 67 weeks or within 16 months). On average 0.9 patients per week were recruited.

Overall, patient recruitment was completed within the estimated period, however the recruitment rate per week was slower from what was initially estimated.

Feasibility of recruiting the targeted sample

During this period, 874 patients with proximal femoral fractures were admitted in Leeds General Infirmary (Figure 6). The majority of these were intracapsular fractures (522 fractures, 60%), followed by intertrochanteric type A1/A2 fractures (235 fractures, 27%) followed by subtrochanteric/reverse oblique (type A3) fractures (89 fractures, 10%) (28 fractures were not classified).

Out of the 253 A1/A2 intertrochanteric fractures, 144 (57%) were screened for the purposes of this trial. The main 2 reasons for patients not to be screened included: 1. A1 type of fractures, 2. Weekend/bank holiday presentations.

The proportion of patients who were approached and participated in the study was 60/69 (87%). In addition to the sixty patients who were randomised, nine patients were approached by the research team, but they did not provide consent (Table 6). Four patients declined participation, two patients did not speak any English, two patients were too anxious to decide about participation prior to surgery and one patient was taken to theatres early in the morning and there was not adequate time for recruiting.

The proportion of patients who were eligible and participated in the study was 60/100 (60%). In addition to the sixty-nine patients who were approached, there were another thirty-one patients who were eligible, but were not approached for consent. The reasons they were not approached were (Table 6): sixteen patients either presented during a weekend or a bank holiday or when no member of the research

team was available, nine patients, although they had an A2 type fracture, a long nail was the recommended implant, three patients presented on a day that a surgeon trained to perform the nail independently was not available, one patient was already in the trial for a previous fracture in the contralateral hip, and for two patients no reason was documented.

The proportion of patients who were screened and participated in the trial was 60/144 (41.7%). In addition to the 100 patients who were eligible, another 44 patients were screened but didn't meet the inclusion criteria. They were excluded for the following reasons: thirteen were older than 95 years old, eleven were not able to walk at least 6m, six had an A1 type fracture, five had eGFR<30, four had poor life expectancy, three had another additional fracture in the ipsilateral leg, one had severe liver disease, and in one patient there was high suspicion for subtrochanteric extension.

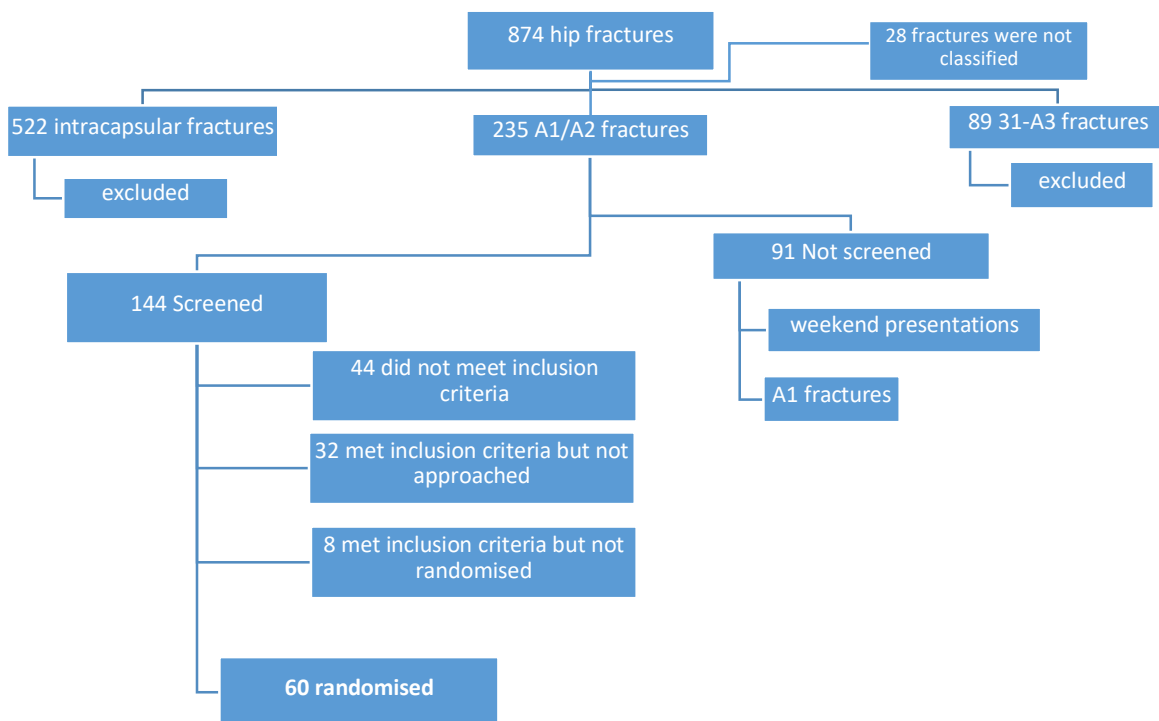


Figure 6: Flow diagram of all patients with hip fractures presented at Leeds General Infirmary during the study period

Table 6: Reasons patients excluded from the study.

| Did not meet inclusion criteria (n) | Not approached (n) | Not randomised (n) |
|---|---|--|
| <ul style="list-style-type: none"> • age >95 or <55 (13) • unable to walk at least 6m (11) • 31-A1 fractures (6) • eGFR<30 (5) • poor life expectancy (4) • ipsilateral concomitant fracture (3) • severe liver disease (1) • suspicion of subtrochanteric extension (1) | <ul style="list-style-type: none"> • research team not available (16) • clinical decision for long nail (9) • surgeon to perform nail not available (3) • unknown reasons (2) • already in trial (1) | <ul style="list-style-type: none"> • patient declined participation (4) • patient did not speak English (2) • patient too anxious to make a decision (2) • lack of time to consent (1) |

7.1.2 Randomisation and other trial procedural issues

All but six patients were randomised through the online randomisation system provided by King's Clinical Trial Unit. Six patients had to be randomised by tossing a coin because the server was down at King's clinical trial unit. Coin toss was performed by staff at King's Clinical Trial Unit. Randomisation results were passed to the research team through the phone and confirmed by email. Although a coin toss could introduce a bias in the randomisation method, it was deemed that it was a reasonable alternative randomisation method by the Kings Clinical Trial Unit scientists but also by the trial statistician.

One patient who was randomised to the nail group received a DHS. This patient was initially planned to go to theatres on a Friday when a surgeon trained to perform the nail procedure was available. However, the patient's surgery was postponed for the next day due to lack of operating time. On Saturday, due to the absence of a surgeon familiar with the nailing kit, the patient received a DHS. This patient was initially kept in the trial (for intention to treat analysis) but was withdrawn by their consultee at week 4 follow-up.

Two of the patients who were randomised to a nail and one patient who was randomised to a DHS received a third treatment, a long intramedullary nail. The operating plan changed intraoperatively because when the patient was positioned onto the traction table the fracture was found to extend in the subtrochanteric area and therefore it was re-classified as type A3 fracture. As a result, those patients were withdrawn, due to ineligible fracture pattern.

Other procedural issues:

One patient had AMTS <8 on admission due to acute confusion. Following their operation, confusion resolved, and their mental test score increased. Therefore, this patient re-gained capacity and was re-consented. Since they did not have dementia, they used the questionnaires for patients without dementia (LEM and LHS instead of DEMQOL).

Two patients despite having AMTS <8, had capacity to give informed consent. They consented themselves for their operation and for participating in the trial. Since they had capacity, it felt appropriate to use the questionnaires for people without cognitive impairment. As a result, these patients used the LEM and LHS questionnaires, but they were included in the AMTS<8 group.

7.2 Primary outcome (TUG time)

To assess whether the TUG test is a good physical assessment tool to be used as a primary outcome in a full scale trial, it was hypothesized that all patients should be able to perform the TUG test at week 4 follow-up.

Out of the 50 patients who attended week 4 follow-up, only 42 (84%) were able to perform the TUG test at least once. Eight patients (16%) were not able to perform the test either because they could not mobilize at all or because they were not able to follow instructions and complete the test.

At 12 weeks, 39/44 (88.6%) of the patients who remained in the trial were able to perform the test. Despite the later time point, 5 patients were not able to complete the test.

Overall, not all the patients were able to perform the TUG test neither at 4 weeks nor at 12 weeks. Missing values of the primary outcome is not ideal and compromises the quality of the data. The TUG test did not meet the criterion set to assess its suitability to be used as a primary outcome and thus a different outcome measure should be pursued as a primary outcome in a future definite trial.

7.3 Retention

The patients flow in the trial is shown in Figure 6.

To assess retention, it was hypothesized that at least 90% of the patients recruited should attend week 4 follow-up.

Out of the 60 patients recruited, 50 (83.3%) patients attended week 4 follow-up (Table 7). Three (5%) patients were withdrawn by the research team because they had a type A3 fracture, one (1.7%) patient was withdrawn by their personal consultee, four died (6.7%), and two (3.3%) patients did not attend their follow-up. Split by AMTS, 34/38 patients (89.5%) with $AMTS \geq 8$ and 16/22 patients (72.7%) with $AMTS < 8$ attended the week 4 visit.

If we exclude the three patients with type A3 fractures, then 50 out of the 57 (87.7%) eligible patients attended week 4 follow-up. Split by AMTS, 34/36 patients (94%) with $AMTS \geq 8$ attended week 4 follow-up, compared to 16/21 (76.2%) with $AMTS < 8$. If all patients still remaining in the trial had attended the week 4 visit, the overall retention rate would have been 52/57 (91%); 36/36 (100%) for those with $AMTS \geq 8$, 15/21 (71%) for those with $AMTS < 8$.

The rates of retention at 12 weeks were 35/38 patients (92.1%) with $AMTS \geq 8$ compared to 14/22 (63.6%) with $AMTS < 8$ (overall 49/60; 81.7%). If we exclude those with type A3 fractures, then 35/36 patients (97.2%) with $AMTS \geq 8$ and 14/21 (66.7%) with $AMTS < 8$. If all patients still remaining in the trial had attended the week 12 visit, the overall retention would be 50/57 (87.7%); 36/36 (100%) for those with $AMTS \geq 8$ and 14/21 (66.7%) for those with $AMTS < 8$.

In total, five patients did not attend their follow up visits; two patients missed week 2 FU, 2 patients missed week 4 FU and 1 patient missed week 12 FU. The main reason that week 2 FU was missed, it was because the patient was discharged home and there was not enough time to organise the FU visit. The window for the 1-week review was one 7 days and the research clinic ran only once a week and as a result, if the patient could not attend that day, the FU should be a week later, which was too late. The reason that patients missed week 4 and week 12 reviews were due to the patients being unreachable (due to provisional change of address). To minimise the risk of missed visits, wider follow up windows or more frequent research clinics or telephone reviews, will need to be considered in a future trial.

In conclusion, it was not feasible to retain the initially targeted percentage of all patients in the trial by week 4 visit. A trial which excluded patients with cognitive impairment would be feasible by this metric,

as >90% with AMTS \geq 8 were retained, but such a trial would not be representative of the target patient population for the intervention.

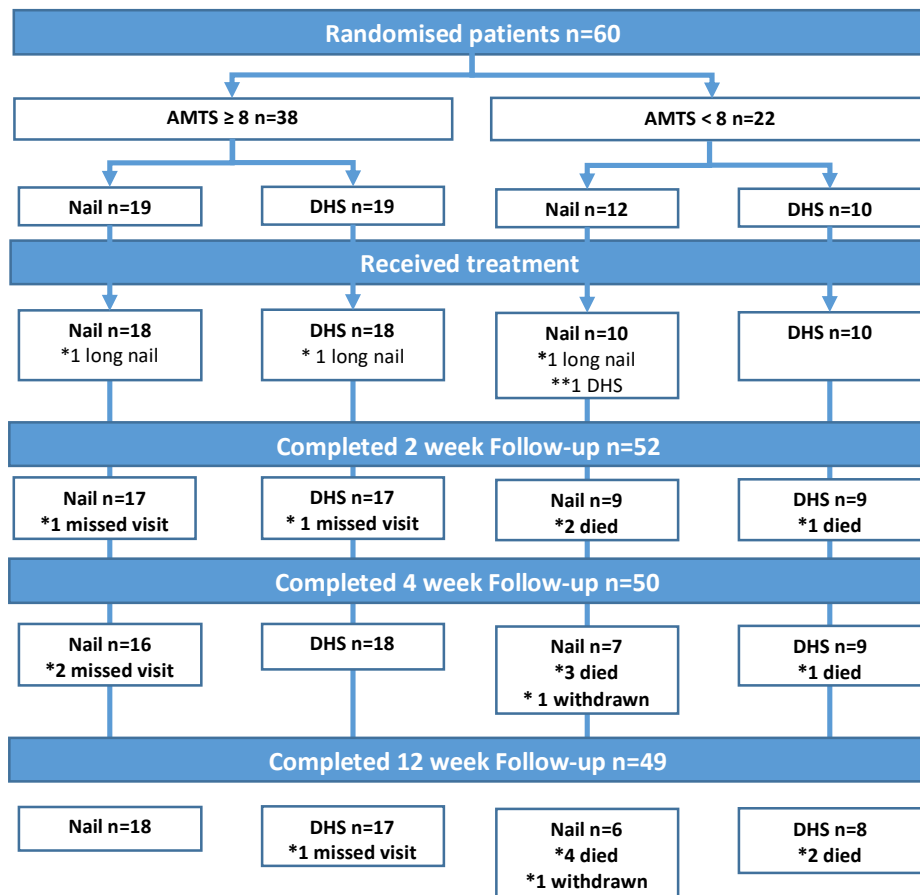


Figure 7: Consort flow diagram of participants as per randomised treatment.

Table 7: Attendance according to treatment received.

| n (%) | AMTS \geq 8 | | | AMTS $<$ 8 | | | All patients |
|----------------------|---------------|-------------|------------|------------|------------|------------|--------------|
| | Nail | DHS | Long nail | Nail | DHS | Long nail | |
| | N=18 | N=18 | N=2 | N=10 | N=11 | N=1 | N=60 |
| Week 2 visit | | | | | | | |
| Attended | 17 (94.4%) | 17 (94.4%) | 0 (0.0%) | 8 (80.0%) | 10 (90.9%) | 0 (0.0%) | 52 (86.7%) |
| DNA | 1 (5.6%) | 1 (5.6%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 2 (3.3%) |
| Withdrawn | 0 (0.0%) | 0 (0.0%) | 2 (100.0%) | 0 (0.0%) | 0 (0.0%) | 1 (100.0%) | 3 (5.0%) |
| Died | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 2 (20.0%) | 1 (9.1%) | 0 (0.0%) | 3 (5.0%) |
| Week 4 visit | | | | | | | |
| Attended | 16 (88.9%) | 18 (100.0%) | 0 (0.0%) | 7 (70.0%) | 9 (81.8%) | 0 (0.0%) | 50 (83.3%) |
| DNA | 2 (11.1%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 2 (3.3%) |
| Withdrawn | 0 (0.0%) | 0 (0.0%) | 2 (100.0%) | 0 (0.0%) | 1 (9.1%) | 1 (100.0%) | 4 (6.7%) |
| Died | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 3 (30.0%) | 1 (9.1%) | 0 (0.0%) | 4 (6.7%) |
| Week 12 visit | | | | | | | |
| Attended | 16 (88.9%) | 17 (94.4%) | 0 (0.0%) | 6 (60.0%) | 7 (63.6%) | 0 (0.0%) | 46 (76.7%) |
| DNA | 0 (0.0%) | 1 (5.6%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 1 (1.7%) |
| Phone FU | 2 (11.1%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 1 (9.1%) | 0 (0.0%) | 3 (5.0%) |
| Withdrawn | 0 (0.0%) | 0 (0.0%) | 2 (100.0%) | 0 (0.0%) | 1 (9.1%) | 1 (100.0%) | 4 (6.7%) |
| Died | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 4 (40.0%) | 2 (18.2%) | 0 (0.0%) | 6 (10.0%) |

7.4 Additional feasibility findings affecting data quality

7.4.1 Data completion rates in key variables

The following variables were considered key: blood loss (in suction and in surgical gauzes), pain NRS, TUG test, LEM, LHS, DEMQOL, radiographic outcomes, LOS, time till ready for discharge, morphine equivalent dose requirements.

Blood loss (in ml from suction and in g from surgical swabs weight)

Out of the 60 patients, these variables were missing in six patients; three patients received a long nail and therefore they were excluded, one patient signed the consent form, withdrew consent prior to surgery and then decided that they would like to participate in the trial (however, blood loss was not measured during surgery), and in two patients there was no reason documented.

Overall, 108/120 values were recorded, and data completeness was 90%.

NRS for pain:

- There were four values missing for the baseline data; three patients were unable to answer the question due to advanced dementia, and one patient went to theatres before completing all baseline questionnaires and since they had a long nail and withdrawn, the NRS for pain was not completed.
- There were ten values missing for week 2 data; three withdrawals due to long nail, three deaths, two patients with dementia who were not able to answer the question, and two patients who missed the window for this visit.
- There were twelve values missing for week 4 data; three withdrawals due to long nail, one withdrawal by personal consultee, four deaths, two patients with dementia who were unable to answer the question and two patients who did not attend the visit.
- There were thirteen values missing for week 12 data; three withdrawals due to long nail, one withdrawal by personal consultee, six deaths, one patient who sustained a patella fracture and therefore the question wasn't asked, one patient with dementia who was unable to answer the question and one patient who did not attend the visit.

Overall, 201/240 values were completed for NRS pain and data completeness was 83.8%.

The TUG test:

- There were twenty-seven missing values at 2 weeks visit; three withdrawals due to long nail, three deaths, two patients who missed the follow-up window and therefore did not attend the visit, fourteen patients who were unable to walk 6m safely, two patients who were unable to perform because they were medically unwell, one patient who was unable to perform due to advanced dementia, one patient who performed with assistance by physio so it was not counted, and one patient who refused to attempt the test.
- There were eighteen missing values at 4 weeks; three withdrawals due to long nail, one withdrawal by personal consultee, four deaths, two patients who did not attend the visit, and eight patients who were unable to walk 6m safely.
- There were twenty-one missing values at 12 weeks; three withdrawals due to long nail, one withdrawal by personal consultee, six deaths, one patient who sustained a patella fracture and therefore the test wasn't attempted, one patient who did not attend the visit, three patients who had a telephone consultation, one patient who was unable to follow instructions, one patient who left from clinic before completing all the visit assessments, and four who were unable to walk 6m safely.

Overall, 114/180 values (63.3%) were complete for the TUG test.

LEM/LHS:

The LEM and LHS questionnaires were given to 41 patients (38 patients with AMTS \geq 8 and three patients with AMTS $<$ 8 who either regained capacity or had capacity but AMTS was $<$ 8).

- There was one missing value from the pre-injury values; one patient went to theatres straight after consent and before they completed all questionnaires. They received a long nail and therefore they were withdrawn, and no further questionnaires were completed.
- There were four values missing from the data at 2 weeks; two withdrawals due to long nail, two patients missed the follow-up window.
- There were four values missing from the data at 4 weeks; two withdrawals due to long nail and two patients did not attend the visit.
- There were four values missing from the data at 12 weeks; two withdrawals due to long nail, one patient did not attend, and one patient put down the phone before all questionnaires were completed.

Overall, 151/164 values (92.1%) were complete.

DEMQOL

This questionnaire was given only to patients with AMTS<8.

- There were five values missing from the pre-injury data; four patients with dementia who were unable to answer the questions and one patient who did not complete the questionnaire before they went to theatres; they received a long nail and therefore they were withdrawn from the study.
- There were six values missing from week 2 data; three patients died, one withdrawal due to long nail, and two patients with dementia who were not able to answer the questions.
- There were seven values missing from week 4 data; four patients died, two withdrawals due to long nails, and one patient with dementia who was unable to answer the questions.
- There were 9 values missing from data from week 12; six patients died, two withdrawals due to long nails, and one patient with dementia who was unable to answer the questions.

Overall, 49/76 values (62%) were complete.

DEMQOL-carer

This questionnaire was completed by a carer or a family member in patients with AMTS<8.

- There were four values missing from the pre-injury data; in two occasions it was impossible to contact a carer or family member, one patient went to theatres before the questionnaire was completed and because they received a long nail and they were subsequently withdrawn, the questionnaire was not completed, and one patient who went to theatre and because they were unwell after surgery it felt inappropriate to give the questionnaire to the patient's family (patient was in end of life care).
- There were four values missing from week 2 data; three patients died, and one withdrawal due to long nail.
- There were six values missing from week 4 data; four patients died, one withdrawal due to long nail, and one withdrawal by their consultee.
- There were eight values missing from week 12 data; six patients died, one withdrawal due to long nail, and one withdrawal by their consultee.

Overall, 54/76 values (71.1%) were complete.

Radiographic variables

Radiographs were taken from each patient attending a follow up visit at 2, 4, and 12 weeks.

- There were eight values missing from week 2 data; three patients died, three withdrawals due to long nail, and two patients missed the window for the week-2 visit and therefore the visit did not take place.
- There were ten values missing from week 4 data; four patients died, three withdrawals due to long nail, one withdrawal by the consultee and two patients did not attend the visit.
- There were fifteen values missing from week 12 data; six patients died, three withdrawals due to long nail, one withdrawal by the consultee, three consultations through the phone, one patient did not attend the visit and one patient left from clinic before all assessments were performed.

Overall, 147/180 values (81.7%) were complete.

Length of stay

- There were seven values missing; three withdrawals due to long nail, and four deaths while patients were still hospitalized.

Overall, 53/60 values (88.3%) were complete.

Readiness to discharge

- There were six values missing; three withdrawals due to long nail, and three patients died before they were deemed ready for discharge.

Overall, 54/60 values (90%) were complete.

Morphine equivalent dose requirements

Analgesia requirements were recorded during the first 2 weeks from surgery. Any newly prescribed opioid-based analgesia given to the patient was included in the overall morphine equivalent dose.

- There were eight values missing; three withdrawals due to long nail, three patients died within 2 weeks, the drug chart was missing from the patient's notes in one case and one patient was excluded as they were on fentanyl patches prior to injury.

Overall, 52/60 values (86.7%) were complete.

In summary, the TUG test had the 2nd lowest data completion rate among the key variables (Table 8). The highest completion rate was for the LEM or LHS; interestingly these outcomes were administered only in patients with AMTS \geq 8. Finally, there was a trend for higher completion rates, in earlier stages of the trial.

Table 8: Data completeness of key variables.

| | Pre-injury | Week 2 | Week 4 | Week 12 | Total |
|--------------------------|------------|--------|--------|---------|-------|
| Blood loss | NA | NA | NA | NA | 90% |
| NRS for pain | 93.3% | 83.3% | 80% | 78.3% | 83.8% |
| TUG test | NA | 55% | 70% | 65% | 63.3% |
| LEM or LHS | 97.6% | 90.2% | 90.2% | 90.2% | 92.1% |
| DEMQOL | 73.7% | 68.4% | 63.2% | 52.6% | 62% |
| DEMQOL carer | 78.9% | 78.9% | 68.4% | 57.9% | 71.1% |
| X-rays | NA | 86.7% | 83.3% | 75% | 81.7% |
| Length of stay | NA | NA | NA | NA | 88.3% |
| Readiness to discharge | NA | NA | NA | NA | 90% |
| Morphine equivalent dose | NA | NA | NA | NA | 86.7% |

To minimize missing data, the following changes can be considered in a future trial:

- Assessing key variable in early stages of the trial.
- Having wide follow-up windows for the research team to have time to arrange the follow-up visits.
- Using questionnaires that can be completed either by the participant or by a carer if the participant is unable to give an answer due to dementia.
- Having telephone reviews as follow-ups since hospital visits are difficult in this cohort of patients. Moreover, completion of questionnaires through post can be considered as an alternative to hospital follow-up visits.
- Having a physical assessment test that is easy to perform (so more people will be able to perform) and will include value '0' in the range of outcomes; this will eliminate the missing values due to the participants being unable to complete the test.

- Documenting every reason why a value was missing when possible.
- Randomising patients during surgery will result in randomising only eligible patients; however, this may cause delays in the theatre team as the theatre team open the trays before patients arrive in the operating room.

7.4.2 AMTS as a screening tool for cognitive impairment

The Abbreviated Mental Test Score (AMTS) is an easy and freely available tool to screen for cognitive impairment. It only takes a couple of minutes to carry out and it is one of the most used screening tools in the literature.

In this study we used the AMTS to screen for dementia. In the UK, AMTS is performed for every patient with proximal femoral fracture routinely. If it is not performed, then the hospital does not receive the maximum payment for that patient.

Three of the patients in this study screened positive for dementia, while they had capacity to make decisions. For this reason, they completed the same type questionnaires that the other patients with capacity (i.e. LEM and LHS). This confusion was possibly created because the process of consent was linked to the AMTS score. According to the protocol "For patients without capacity to consent (dementia, AMTS score<8), informed consent will be obtained as set out in the guideline, Mental Capacity Act 2005." Although the AMTS is a good tool for screening for cognitive impairment or dementia, it is not a tool to assess capacity. A person is capable of making decisions for themselves if they are able to understand the information given to them, they are able to retain and weigh this information in order to make a decision and they are able to communicate their decision. People with mild cognitive impairment may still have capacity and decide for their own treatment. Therefore, an AMTS<8 doesn't always mean that the people lack capacity, but it indicates that this person has a degree of cognitive impairment.

To avoid similar confusion in future, it needs to be clear, that the AMTS will only be used to stratify for dementia during randomisation process and to determine which functional outcome scores will be used.

Another issue was with patients who lacked capacity on admission but after surgery, they would regain capacity (e.g. acute confusion or delirium). According to the protocol, these patients had to provide new written informed consent. Since they had capacity, the LEM and the LHS questionnaires were used. Similarly, whether they have capacity to make decisions for their treatments should not be linked to their AMTS and they should have used the questionnaires that apply to their original AMTS group.

Finally, another limitation of the AMTS is that it can fluctuate with time, as patient's level of cognition can be affected from acute conditions, such as infection and delirium. As a result, a patient may be admitted in the hospital confused due to infection and after a couple of days they may be lucid after appropriate treatment. For the purposes of this study, it was accepted that patients would remain in the initial AMTS group, even though the AMTS could improve later during the hospital stay.

7.4.3 Negative values in the radiographic outcomes

While analysing the results of radiographic outcomes, we observed that some results would not agree with clinical observations. This applied to the screw collapse (which was calculated by comparing the length of the cephalic screw between 2 visits).

Normally, it is expected for the neck length to be maintained or to collapse. Any lengthening of the neck cannot be interpreted clinically. It was observed that 13/47 of neck collapse calculations, the values were negative at week 4 and 13/43 of calculations at week 12. All measurements were performed by two assessors independently and any discrepancies were resolved by a 3rd assessor. The method above has minimized the risk of measurement error but also the risk of any interobserver error. The only realistic explanation is that the differences were due different angles and different projections of the X-rays taken. Realistically it is impossible to obtain exactly the same view in two different routine X-rays. To address this in the analysis, zero values were imputed for any negative values. This is suboptimal.

7.5 Feasibility conclusions

- It was possible to recruit 60 patients with a pertrochanteric fracture (AO/OTA 31A2).
- It was not feasible to use the TUG test as a primary outcome measure because of the large number of missing values due to patients being unable to perform it.
- There were issues with randomisation; in a future trial randomisation should occur as late as possible, ideally during surgery, to avoid ineligible patients being included. However, this may cause delays in the theatre team as the theatre team open the trays before the patients arrives in the operating room.
- Overall, it was not feasible to retain 90% of all patients in the trial by week 4; This was only feasible for patients with AMTS \geq 8.
- Other physical ability outcome measure tools will need to be considered to assess functional mobility. Ideally, a physical assessment tool should require minimum physical effort and should have a value for patients who were not able to perform it.
- However, given that patients struggled to perform the TUG trial at least once at all time points, even those with AMTS \geq 8, these functional tests may need to be completed at a later stage. Although rates of retention were good for patients with AMTS \geq 8, suggesting later follow-up would not be a problem in this group, later follow-up will be very difficult for the patients with AMTS $<$ 8 due to the high level of attrition observed at the later stages in the trial.
- To minimize missing data in a future trial, consideration could be given to:
 - Using wider follow-up windows, provided these would not impact on the integrity of the results.
 - Having more telephone reviews since hospital visits are difficult in this group of patients.
 - Completion of questionnaires online or through post could be considered as an alternative to hospital follow up visits, although resources would need to be dedicated to ensuring acceptable completion rates.
- To address attrition issues relating to mental capacity and collection of patient-reported outcomes, alternative PROMS should be sought. The ideal PROM should be completed by both patients with cognitive impairment and without. For this reason, PROMs with available proxy-questionnaires would fit best this purpose. Moreover, a PROM that would include a value for a deceased patient will minimise the data lost due to attrition.

7.6 Efficacy results

7.6.1 Baseline patient characteristics

Baseline patient characteristics by randomised group are shown in Table 9. In this analysis, the principle of intention to treat was followed.

Statistical analysis to identify any baseline imbalance between the groups was not performed as per the CONSORT 2010 statement (123). Such analyses are illogical because the groups are randomised; any apparent differences between the groups at baseline can have only arisen by chance.

Patient demographics:

- The average age was 84.9 years old (SD: 7.3, range: 56 – 95).
- There were 12 (20%) males and 48 (80%) females.
- All patients were white British.

Comorbidities:

Eighteen patients (30%) had ASA score 2, 37 patients (61.7%) had score ASA 3 and 5 (8.3%) patients had ASA score 4.

Detailed patients' comorbidities are shown on Table 10.

Both groups had comparable Charlson comorbidity index (nail 5.3 vs DHS 5.1). Patients with AMTS \geq 8 had an average Charlson score 4.7 whereas patients with AMTS <8 had an averages Charlson index 6.1.

Pre-injury place of residence:

Prior to injury, 48 patients (80%) lived in their own home, 1 (1.7%) lived with family, 9 (15%) lived in a residential care home and 2 (3.3%) in a nursing home.

Pre-injury level of mobility:

Nineteen (31.7%) patients were able to mobilize without any mobility aid and 41 (68.3%) required a mobility aid; 22 (36.7%) required one stick, 17 (28.3%) required a frame (the mobility aid was not recorded in 2 cases).

Table 9: Screening variables according to randomised treatment.

| | AMTS \geq 8 | | AMTS $<$ 8 | | All patients N=60 |
|-----------------------------------|---------------|-------------|--------------|-------------|----------------------|
| | Nail N=19 | DHS N=19 | Nail N=12 | DHS N=10 | |
| Age, mean (SD) | 84.5 (5.7) | 81.5 (9.9) | 87.6 (3.9) | 88.9 (3.4) | 84.9 (7.3) |
| Sex, n (%) | | | | | |
| Male | 6 (31.6%) | 4 (21.1%) | 0 (0.0%) | 2 (20.0%) | 12 (20.0%) |
| Female | 13 (68.4%) | 15 (78.9%) | 12 (100.0%) | 8 (80.0%) | 48 (80.0%) |
| Ethnicity, n (%) | | | | | |
| White British | 19 (100.0%) | 19 (100.0%) | 12 (100.0%) | 10 (100.0%) | 60 (100.0%) |
| Residential status, n (%) | | | | | |
| Own home | 18 (94.7%) | 18 (94.7%) | 6 (50.0%) | 6 (60.0%) | 48 (80.0%) |
| Family | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 1 (10.0%) | 1 (1.7%) |
| Residential | 1 (5.3%) | 1 (5.3%) | 4 (33.3%) | 3 (30.0%) | 9 (15.0%) |
| Nursing | 0 (0.0%) | 0 (0.0%) | 2 (16.7%) | 0 (0.0%) | 2 (3.3%) |
| Pre-injury mobility, n (%) | | | | | |
| No aids | 8 (42.1%) | 5 (26.3%) | 3 (25.0%) | 3 (30.0%) | 19 (31.7%) |
| Walking aid | 11 (57.9%) | 14 (73.7%) | 9 (75.0%) | 7 (70.0%) | 41 (68.3%) |
| Mobility status, n (%) | | | | | |
| No aids required | 8 (42.1%) | 5 (26.3%) | 3 (25.0%) | 3 (30.0%) | 19 (31.7%) |
| One stick/crutch | 6 (31.6%) | 10 (52.6%) | 3 (25.0%) | 3 (30.0%) | 22 (36.7%) |
| Frame | 5 (26.3%) | 3 (15.8%) | 6 (50.0%) | 3 (30.0%) | 17 (28.3%) |
| Aid type unknown | 0 (0.0%) | 1 (5.3%) | 0 (0.0%) | 1 (10.0%) | 2 (3.3%) |
| ASA score, n (%) | | | | | |
| 2 | 7 (36.8%) | 9 (47.4%) | 2 (16.7%) | 0 (0.0%) | 18 (30.0%) |
| 3 | 10 (52.6%) | 10 (52.6%) | 7 (58.3%) | 10 (100.0%) | 37 (61.7%) |
| 4 | 2 (10.5%) | 0 (0.0%) | 3 (25.0%) | 0 (0.0%) | 5 (8.3%) |
| Charlson score, mean (SD) | 4.9 (1.0) | 4.5 (1.4) | 6.1(1.4) | 6.2(1.2) | 5.25(1.4) |

Table 10: Comorbidities according to randomised group.

| | AMTS \geq 8 | | AMTS $<$ 8 | | Total |
|---|---------------|-------------|-------------|-------------|--------------|
| | Nail | DHS | Nail | DHS | |
| n/N (%) | N=19 | N=19 | N=12 | N=10 | N=60 |
| Ischemic Heart Disease (IHD) | 5/19 (26.3) | 3/19 (15.8) | 5/12 (41.7) | 3/10 (30.0) | 16/60 (26.7) |
| Arrhythmia | 5/19 (26.3) | 6/19 (31.6) | 4/12 (33.3) | 2/10 (20.0) | 17/60 (28.3) |
| Heart Failure | 2/19 (10.5) | 2/19 (10.5) | 0/12 (0.0) | 1/10 (10.0) | 5/60 (8.3) |
| Hypertension | 9/19 (47.4) | 5/19 (26.3) | 6/12 (50.0) | 2/10 (20.0) | 22/60 (36.7) |
| Heart valve disease | 2/19 (10.5) | 1/19 (5.3) | 0/12 (0.0) | 1/10 (10.0) | 4/60 (6.7) |
| Pulmonary disease (COPD, asthma, TB, PE) | 5/19 (26.3) | 7/19 (36.8) | 2/12 (16.7) | 4/10 (40.0) | 18/60 (30.0) |
| Diabetes | 5/19 (26.3) | 1/19 (5.3) | 3/12 (25.0) | 3/10 (30.0) | 12/60 (20.0) |
| Thyroid disease | 2/19 (10.5) | 5/19 (26.3) | 2/12 (16.7) | 2/10 (20.0) | 11/60 (18.3) |
| Other endocrine disease | 0/19 (0.0) | 1/19 (5.3) | 0/12 (0.0) | 0/10 (0.0) | 1/60 (1.7) |
| Neurological disease | 5/19 (26.3) | 3/19 (15.8) | 2/12 (16.7) | 2/10 (20.0) | 12/60 (20.0) |
| Osteoporosis | 8/19 (42.1) | 6/19 (31.6) | 1/12 (8.3) | 3/10 (30.0) | 18/60 (30.0) |
| Previous hip fracture | 0/19 (0.0) | 0/19 (0.0) | 3/12 (25.0) | 0/10 (0.0) | 3/60 (5.0) |
| Inflammatory disease | 0/19 (0.0) | 2/19 (10.5) | 2/12 (16.7) | 0/10 (0.0) | 4/60 (6.7) |
| Malignancy | 2/19 (10.5) | 1/19 (5.3) | 0/12 (0.0) | 2/10 (20.0) | 5/60 (8.3) |
| Chronic kidney disease | 5/19 (26.3) | 1/19 (5.3) | 2/12 (16.7) | 0/10 (0.0) | 8/60 (13.3) |

COPD=Chronic Obstructive Pulmonary Disease; DHS=Dynamic Hip Screw; PE=Pulmonary embolism; TB=Tuberculosis

7.6.2 Surgery related results

All fractures except one had closed reduction. The only fracture that required open reduction was in the nail group. In order to ensure consistency in the recording of the operating time, the extra time required for reduction of the fracture was deducted from the overall operating time for this patient.

Efficacy analysis was performed with the intention to treat (groups as per randomised treatment), except all radiographic results which are presented according to treatment received.

All surgery related results are shown on Table 11.

Duration of surgery

The mean duration of surgery was similar between the two groups (46.2min vs 48.9min, $p=0.440$).

Blood loss – in ml

The mean blood loss recorded in the suction tubes was descriptively higher (but not statistically significant) in the DHS group than in the nail group (126.7ml vs 83.2ml, $p=0.068$).

Blood loss – weight of swabs

The mean intraoperative weight of swabs was similar in the two groups (79.1 vs 76.6g, $p=0.911$).

Blood transfusion requirements within the first 2 weeks

Slightly a higher percentage of patients in the DHS group (15/28 or 53.6%) than in the nail group (13/29 or 44.8%) required at least 1-unit blood transfusion within the first 2 weeks from surgery ($p=0.600$). However, the difference between the groups was not statistically significant.

It is worth mentioning that there were more patients with preoperative $Hb < 10$ in the nail group than in the DHS group (5 vs 1); however, as these were randomised groups, this difference will have risen by chance, and it is likely due to the relatively small size of this trial. This imbalance in the groups may have made it more difficult for a difference between the groups to become apparent.

Intraoperative complications

There was only one intraoperative complication which occurred in a patient who received a nail. The distal locking screw was not inserted through the nail. Although an intraoperative x-ray was taken intraoperatively to check the position of the screw, it did not become apparent that the screw missed the nail. This became obvious in week 2 follow-up. Patient completed the study and remained under follow-up beyond the 12-week period of the study. Eventually the fracture fixation failed (varus collapse, screw cut through) and the superior cephalic femoral screw was removed under local anaesthetic and sedation. The patient was not fit for any further surgery and therefore no further action was taken.

7.6.3 Days until ready for discharge and length of stay

The time till ready to discharge and the length of stay are shown in Table 11.

Readiness to discharge

This variable was highly skewed; the median time till ready for discharge was descriptively higher in the DHS group than in the nail group (12 days vs 9 days, $p=0.121$).

Further analysis as per AMTS score showed that although the medians were similar between the groups in the $AMTS \geq 8$ subgroup (median 7.0 days in the nail group vs 9.0 days in the DHS group, $p=0.877$), the median readiness for discharge was significantly higher in the DHS group than in the nail group in the $AMTS < 8$ subgroup (median 11.0 days in the nail group vs 20.0 days in the DHS group, $p=0.043$).

Length of hospital stay (LOS)

This variable was highly skewed; the median LOS was descriptively shorter in the nail group than in the DHS group (21.0 vs 22.0, $p=0.187$).

Table 11: Surgery related results and hospital stay.

| | Treatment randomised | | Mean Difference (95% Confidence Interval) | p-value |
|--|-------------------------|-------------------------|--|---------|
| | Nail, n=29 | DHS, n=28 | | |
| Operation time (min) | | | | |
| Mean±SD | 46.2±12.5, n=29 | 48.9±13.5, n=28 | -2.7 (-9.6, 4.2) | 0.440 |
| Blood loss in suction (ml) | | | | |
| Mean±SD | 83.2±66.5, n=28 | 126.7±102.6, n=26 | -43.5 (-90.4, 3.4) | 0.068 |
| Weight of swabs (grams) | | | | |
| Mean±SD | 76.6±65.8, n=28 | 79.1±33.6, n=26 | -2.5 (-47.6, 42.7) | 0.911 |
| Blood transfusion units post-op, n(%) | | | | |
| 0 | 16/29 (55.2) | 13/28 (46.4) | | 0.600 |
| 1 | 1/29 (3.4) | 2/28 (7.1) | | |
| 2 | 10/29 (34.5) | 12/28 (42.9) | | |
| 3 | 2/29 (6.9) | 0/28 (0.0) | | |
| 4 | 0/29 (0.0) | 1/28 (3.6) | | |
| Intra-op complications, n/N (%) | | | | |
| Yes | 1/29 (3.4) | 0/28 (0.0) | | 1.000 |
| No | 28/29 (96.6) | 28/28 (100) | | |
| Days until ready for discharge | | | | |
| Median (range), n | 9.0 (2.0, 27.0), n=27 | 12.0 (1.0, 47.0), n=27 | | 0.121 |
| AMTS≥8 | 7.0 (4.0, 27.0), n=18 | 9.0 (1.0, 25.0), n=18 | | 0.877 |
| AMTS<8 | 11.0 (2.0, 15.0), n=9 | 20.0 (10.0, 47.0), n=9 | | 0.043 |
| In-hospital length of stay, days | | | | |
| Median (range), n | 21.0 (9.0, 72.0), n=26 | 22.0 (10.0, 55.0), n=27 | | 0.187 |
| AMTS≥8 | 20.5 (18.0, 33.0), n=18 | 22.0 (15.0, 23.0), n=18 | | 0.355 |
| AMTS<8 | 30.5 (20.5, 43.5), n=8 | 23.0 (20.0, 25.0), n=9 | | 0.302 |

7.6.4 Analgesia requirements within the first 2 weeks

Patients treated with a DHS had descriptively higher morphine equivalent requirements than patients treated with a nail (median morphine equivalent requirements 91mg vs 72.3mg, $p=0.203$) within the first 2 weeks from surgery (Table 12).

Table 12: Analgesia requirements.

| | | Treatment randomised | | |
|-------------------------------------|-------------------|-------------------------|-------------------------|---------|
| | | Nail, N=29 | DHS, N=28 | p-value |
| Morphine equivalent dose, mg | Median (range), n | 72.3 (0.0, 564.0), n=26 | 91.0 (3.75, 1400), n=26 | 0.203 |

7.6.5 TUG test

Similar proportion of patients treated with a nail and with a DHS were able to complete the TUG test at 2-, 4- and 12 weeks (Table 13).

Table 13: Proportion of patients able to complete ≥ 1 TUG trial according to treatment.

| n/N (%) | Treatment | | p-value |
|---|--------------|--------------|---------|
| | Nail N=29 | DHS N=28 | |
| TUG test trials completed at week 2 | | | |
| 0 | 12/26 (46.2) | 7/26 (26.9) | 0.150 |
| ≥ 1 | 14/26 (53.8) | 19/26 (73.1) | |
| TUG test trials completed at week 4 | | | |
| 0 | 2/23 (8.7) | 6/27 (22.2) | 0.193 |
| ≥ 1 | 21/23 (91.3) | 21/27 (77.8) | |
| TUG test trials completed at week 12 | | | |
| 0 | 2/20 (10.0) | 3/24 (12.5) | 0.795 |
| ≥ 1 | 18/20 (90.0) | 21/24 (87.5) | |

Significantly more patients with $AMTS \geq 8$ were able to perform the TUG test than patients with $AMTS < 8$ at week 2 (Table 14). There were no significant changes in week 4 and 12.

Table 14: Proportion of patients able to complete ≥ 1 TUG trial according to AMTS.

| n/N (%) | AMTS | | p-value |
|---|-----------------------|--------------------|---------|
| | AMTS ≥ 8 N=29 | AMTS < 8 N=28 | |
| TUG test trials completed at week 2 | | | |
| 0 | 8/34 (23.5) | 11/18 (61.1) | 0.014 |
| ≥ 1 | 26/34 (76.5) | 7/18 (38.9) | |
| TUG test trials completed at week 4 | | | |
| 0 | 5/34 (14.7) | 3/16 (18.8) | 0.699 |
| ≥ 1 | 29/34 (85.3) | 13/16 (81.3) | |
| TUG test trials completed at week 12 | | | |
| 0 | 2/32 (6.3) | 3/12 (25) | 0.081 |
| ≥ 1 | 30/32 (93.8) | 9/12 (75) | |

TUG times**Week 2:**

TUG times were comparable between the groups at 2 weeks. The median TUG time was 75.0 sec in the nail group and 120.0 sec in the DHS group ($p=0.585$).

Week 4:

TUG times were comparable between the groups at 4 weeks. The median time was 59.0 sec in the nail group and 51.0 sec in the DHS group ($p=0.669$).

Week 12:

TUG times were comparable between the groups at 12 weeks. The median time was 37.5 sec in the nail group and 31.0 sec in the DHS group ($p=0.317$).

Table 15: Timed Up and GO times.

| | | Treatment randomised | | |
|----------------|-------------------|--------------------------|---------------------------|---------|
| | | Nail | DHS | p-value |
| Week 2 | Median (range), n | 75.0 (20.0, 177.0), n=14 | 120.0 (20.0, 295.0), n=19 | 0.585 |
| Week 4 | Median (range), n | 59.0 (16.0, 381.0), n=21 | 51.0 (13.0, 329.0), n=21 | 0.669 |
| Week 12 | Median (range), n | 37.5 (16.0, 229.0), n=18 | 31.0 (14.0, 119.0), n=21 | 0.317 |

7.6.6 Patient-reported outcomes

1. Pain numeric rating scale (NRS)

Week 2:

Patients who were treated with a nail had significantly lower levels of pain than patients who were treated with a DHS (median NRS 5 vs 7.5, $p=0.003$) at 2 weeks.

Week 4:

Patients who were treated with a nail had descriptively lower levels of pain than patients who were treated with a DHS (median NRS 5 vs 7, $p=0.074$) at 4 weeks.

Week 12:

Patients who were treated with a DHS had descriptively lower levels of pain than patients who were treated with a nail (median NRS 2 vs 3.5, $p=0.795$) at 12 weeks.

Table 16: Pain Numeric Rating Scale.

| | | Nail | DHS | p-value |
|----------------|-------------------|-----------------------|-----------------------|---------|
| Pre-op | Median (range), n | 8.0 (0.0, 10.0), n=27 | 8.0 (0.0, 10.0), n=27 | 0.967 |
| Week 2 | Median (range), n | 5.0 (0.0, 9.0), n=24 | 7.5 (2.0, 10.0), n=26 | 0.003 |
| Week 4 | Median (range), n | 5.0 (0.0, 8.0), n=22 | 7.0 (0.0, 10.0), n=26 | 0.074 |
| Week 12 | Median (range), n | 3.5 (0.0, 8.0), n=22 | 2.0 (0.0, 0.0), n=25 | 0.795 |

2. Lower Extremity Measure (LEM)

Week 2:

Patients who were treated with a nail had descriptively higher LEM scores than patients who were treated with a DHS (medians 41.7 vs 31.3, $p=0.403$).

Week 4:

Patients who were treated with a nail reported higher LEM scores than patients who were treated with a DHS (medians 48.2 vs 43.1, $p=0.595$).

Week 12:

Patients who were treated with a nail reported higher LEM scores than patients who were treated with a DHS (medians 61.3 vs 54.2, $p=0.903$).

Table 17: Lower Extremity Measure.

| Median (range), n | Nail | DHS | p-value |
|-------------------|--------------------------|--------------------------|---------|
| LEM Week 0 | 59.5 (31.3, 100.0), n=18 | 69.2 (48.3, 100.0), n=18 | 0.208 |
| LEM Week 2 | 41.7 (9.8, 73.3), n=17 | 31.3 (11.6, 87.5), n=17 | 0.403 |
| LEM Week 4 | 48.2 (8.62, 77.4), n=16 | 43.1 (14.3, 78.6), n=18 | 0.595 |
| LEM Week 12 | 61.3 (11.2, 84.8), n=18 | 54.2 (5.0, 89.8), n=17 | 0.903 |

3. The London Handicap Scale (LHS)

Week 2:

Both groups had similar median LHS score at 2 weeks (0.6 vs 0.6, $p=0.403$).

Week4:

Both groups had similar median LHS score at 4 weeks (0.6 vs 0.7, $p=0.761$).

Week 12:

Both groups had similar median LHS score at 12 weeks (0.7 vs 0.7, $p=0.804$).

Table 18: London Handicap Score.

| Median (range), n | Nail | DHS | p-value |
|----------------------|----------------------|----------------------|---------|
| London Score Week 0 | 0.7 (0.5, 1.0), n=18 | 0.7 (0.5, 1.0), n=18 | 0.402 |
| London Score Week 2 | 0.6 (0.4, 0.8), n=17 | 0.6 (0.4, 0.8), n=17 | 0.403 |
| London Score Week 4 | 0.6 (0.4, 0.8), n=16 | 0.7 (0.5, 0.8), n=18 | 0.761 |
| London Score Week 12 | 0.7 (0.3, 0.9), n=18 | 0.7 (0.5, 1.0), n=17 | 0.804 |

4. Dementia Quality of Life (DEMQOL)

Week 2:

Patients who received a nail reported higher DEMQOL score than patients who received a DHS (median 89 vs 75.5), but this was not a significant difference.

Similarly, DEMQOL-carer was higher in the nail group than in the DHS group (median 98 vs 92), but not statistically significant.

Week4:

Patients who received a DHS reported higher DEMQOL score than patients who received a nail (median 88.5 vs 87.4), but this was not a significant difference.

In contrary, DEMQOL reported by carers was higher in the nail group than in the DHS group (median 103 vs 92.9), but this was not a significant difference.

Week 12:

Patients who received a nail reported higher DEMQOL score than patients who received a DHS (median 95 vs 85), but this was not a significant difference.

Similarly, DEMQOL reported by carers was higher in the nail group than the DHS group (median 98.5 vs 86), but this was not a significant difference.

Table 19: Dementia Quality of Life.

| Median (range), n | Nail | DHS | p-value |
|----------------------|--------------------------|-------------------------|---------|
| DEMQOL Week 0 | 87.0 (69.0, 95.0), n=5 | 73.6 (40.0, 108.0), n=9 | 0.350 |
| DEMQOL carer Week 0 | 99.2 (84.0, 117.0), n=7 | 97.6 (64.0, 115.0), n=8 | 0.642 |
| DEMQOL Week 2 | 89.0 (66.0, 106.0), n=5 | 75.5 (48.0, 112.0), n=8 | 0.714 |
| DEMQOL carer Week 2 | 98.0 (90.0, 106.0), n=7 | 92.0 (77.0, 115.0), n=8 | 0.599 |
| DEMQOL Week 4 | 84.7 (61.0, 103.0), n=4 | 88.5 (66.0, 112.0), n=8 | 0.671 |
| DEMQOL carer Week 4 | 103.0 (93.0, 111.0), n=5 | 92.9 (79.0, 113.0), n=8 | 0.464 |
| DEMQOL Week 12 | 95.0 (84.0, 111.0), n=3 | 85.0 (60.0, 107.0), n=7 | 0.305 |
| DEMQOL carer Week 12 | 98.5 (65.0, 114.0), n=4 | 86.0 (73.0, 110.0), n=7 | 0.507 |

7.6.7 Mobility at 12 weeks

Level of mobility (Table 18)

At 12 weeks:

There were no differences in the level of mobility between the groups ($p=0.563$). More specifically:

- 1 patient (4.3%) in the nail group was able to mobilize without mobility aids.
- 4 patients (17.4%) in the nail group and 5 patients (20%) in the DHS group were able to mobilize with one stick or crutch.
- 3 patients (13%) in the nail group and 1 patient (4%) in the DHS group were able to mobilize with two sticks or crutches.
- 13 patients (56.5%) in the nail group and 17 patients (68%) in the DHS group were able to mobilize with a frame.
- 2 patients (8.7%) in the nail group and 1 patient (4%) in the DHS group were able to mobilize with a wheelchair.
- 1 patient (4%) in the DHS group was bedridden.

Return to baseline mobility level (Table 18)

Overall, only 14 out of 48 patients (29.2%) returned to their pre-injury mobility levels (Table 18).

Similar percentage of patients returned to their baseline mobility level in the nail and DHS group (7/23, 30.4% vs 7/25, 28.0%, $p=0.852$).

Return to walking

Similar percentages of patients were able to walk at 12 weeks in the nail and DHS group (nail: 21/23, 91.3% vs DHS: 23/25, 92%).

7.6.8 Place of residence at 12 weeks

Place of residence (Table 18)

At 12 weeks, there were no differences in the place of residence between the groups (0.848). More specifically:

- 15 patients (65.2%) in the nail group and 16 patients (64%) in the DHS group lived in their own home.
- 1 patient (4.3%) in the nail group and 1 patient (4%) in the DHS group lived with family.
- 5 patients (21.7%) in the nail group and 6 patients (24%) in the DHS group lived in a residential home.
- 2 patients (8.7%) in the nail group and 1 patient (4%) in the DHS group lived in a nursing home.
- 1 patient (4%) only in the DHS group was still in the hospital.

Change in residential status (Table 18)

Out of the 48 patients who used to live in the own home pre-injury, 31 (64.6%) returned to their own home by week 12 (Table 18).

Similar proportions of patients in both groups returned to their pre-injury place of residence (Nail: 17/23, 73.9% vs DHS: 17/25, 68.0%, $p=0.652$).

Table 20: Mobility and residential status at 12 weeks.

| | Treatment randomised | | p-value |
|---|----------------------|--------------|---------|
| | Nail | DHS | |
| Mobility status at 12-week visit, n/N (%) | | | 0.563 |
| No aids required | 1/23 (4.3) | 0/25 (0.0) | |
| One stick/crutch | 4/23 (17.4) | 5/25 (20.0) | |
| Two sticks/crutches | 3/23 (13.0) | 1/25 (4.0) | |
| Frame | 13/23 (56.5) | 17/25 (68.0) | |
| Wheelchair | 2/23 (8.7) | 1/25 (4.0) | |
| Bedridden | 0/23 (0.0) | 1/25 (4.0) | |
| Mobility status summary, n/N (%) | | | 0.930 |
| In wheelchair/bedridden | 2/23 (8.7) | 2/25 (8.0) | |
| On feet | 21/23 (91.3) | 23/25 (92.0) | |
| Change in mobility, n/N(%) | | | 0.852 |
| Worse | 16/23 (69.6) | 18/25 (72.0) | |
| Returned to pre-BL/improved | 7/23 (30.4) | 7/25 (28.0) | |
| Residential status at 12-week visit, n/N (%) | | | 0.848 |
| Own home | 15/23 (65.2) | 16/25 (64.0) | |
| Family | 1/23 (4.3) | 1/25 (4.0) | |
| Residential | 5/23 (21.7) | 6/25 (24.0) | |
| Nursing | 2/23 (8.7) | 1/25 (4.0) | |
| Other | 0/23 (0.0) | 1/25 (4.0) | |
| Residential status summary, n/N (%) | | | 0.929 |
| Other | 8/23 (34.8) | 9/25 (36.0) | |
| Own home | 15/23 (65.2) | 16/25 (64.0) | |
| Change in residential status, n/N (%) | | | 0.652 |
| Not returned to pre-BL | 6/23 (26.1) | 8/25 (32.0) | |
| Returned to pre-BL | 17/23 (73.9) | 17/25 (68.0) | |

7.7 Radiographic outcomes

Analysis of radiographic variables was performed based on the treatment received.

All radiographs were calibrated prior to any measurements were taken.

7.7.1 Interobserver reliability

All radiographic measurements were taken by 2 clinicians independently. Quality of the data was assessed by calculating the interclass correlation coefficient. Since the measurements were taken only once by each assessor, the intraobserver correlation was not assessed.

As shown in Table 21, all measurements had excellent interobserver reliability. The lowest agreement was for the TAD measurement; despite the lowest interclass correlation coefficient, the level of agreement was still very good (interclass correlation coefficient 0.820).

The high level of agreement was probably due to the fact that the opinion of a third assessor was sought if there was big discrepancy in the measurements of the two assessors.

Radiographic outcome results are shown on Table 22.

Table 21: Interobserver correlation of radiographic measurements.

| | Interclass correlation coefficient | 95% Confidence interval (lower, upper bound) | p-value |
|-------------------------------|------------------------------------|--|---------|
| Proximal screw length Week 2 | 0.997 | 0.994, 0.998 | <0.001 |
| Distal screw length Week 2 | 0.991 | 0.968, 0.997 | <0.001 |
| Proximal screw length Week 4 | 0.997 | 0.994, 0.998 | <0.001 |
| Distal screw length Week 4 | 0.991 | 0.954, 0.997 | <0.001 |
| Proximal screw length Week 12 | 0.996 | 0.992, 0.998 | <0.001 |
| Distal screw length Week 12 | 0.993 | 0.982, 0.997 | <0.001 |
| TAD | 0.820 | 0.683, 0.898 | <0.001 |
| CCD week 2 | 0.929 | 0.875, 0.960 | <0.001 |
| CCD week 4 | 0.944 | 0.902, 0.969 | <0.001 |
| CCD week 12 | 0.939 | 0.890, 0.967 | <0.001 |
| Medialisation week 2 | 0.914 | 0.835, 0.953 | <0.001 |
| Medialisation week 4 | 0.925 | 0.851, 0.961 | <0.001 |
| Medialisation week 12 | 0.957 | 0.896, 0.979 | <0.001 |

7.7.2 Tip-apex distance - TAD

The mean TAD was less than 25 in both groups; however, patient treated with a nail had significantly higher TAD than patients treated with a DHS group (18.2mm vs 14.9mm, $p=0.044$).

Moreover, there were 4 patients (15.4%) in the nail group with TAD >25mm whereas none in the DHS group.

7.7.3 Neck-shaft angle

The average neck-shaft angle was statistically significantly lower in the nail group than in the DHS group at each follow-up visit (Table 20). However, the change in the neck-shaft angle between week 2 and week 12 was similar between the groups (change: nail = 0.8mm, DHS = 0.1mm, $p=0.490$). Moreover, the change of the neck-shaft angle within each group did not change significantly throughout the study period.

7.7.4 Femoral neck shortening

Femoral neck shortening was measured using two different techniques:

- A. Neck collapse was measured as the collapse of the cephalic screws (nail) or the lag screw (DHS) at 4 weeks and 12 weeks.

In the nail group, the mean collapse of the proximal screw was 1.7mm at week 4 and 2.5mm at week 12. The mean collapse for the distal cephalic screw was 2mm at week 4 and 3.3mm at week 12.

In the DHS group, the mean screw collapse was 2.3mm at week 4 and 3.7mm at week 12.

The differences between the groups were not statistically significant (Table 20).

- B. Neck collapse was measured as the length of a line starting from the apex of the femoral head and finishing at the lateral border of the femur and coming through the middle of the neck. This distance was compared to a similar distance of the contralateral native hip (patients with joint replacements were excluded). Any difference between the two hips was considered due to neck shortening.

The neck collapse measured with this technique was statistically significant less in the nail group at all time points (at week-2 1.2mm vs 9.5mm, $p<0.01$, at week-4 3.4mm vs 10.6mm, $p=0.001$, at 12-weeks 2.9mm vs 12.2mm, $p=0.001$).

7.7.5 Medial displacement of the fracture

Medialisation (medial displacement of the fracture) was assessed by assessing the amount of medialisation but also by calculating the proportion of patients with significant medialisation (i.e. >5mm).

Medialisation was less in the nail group than in the DHS group at each time point:

- At 2 weeks: 2.6mm vs 5mm, $p=0.007$.
- At 4 weeks: 2.3mm vs 5.8mm, $p<0.001$.
- At 12 weeks 2.7mm vs 5.8mm, $p=0.016$.

Moreover, more patients in the DHS group had medialisation >5mm:

- At 2 weeks: 15/27 (55.6%) vs 3/25 (12%), $p=0.003$.
- At 4 weeks: 16/26 (61.5%) vs 3/23 (13%), $p=0.001$.
- At 12 weeks: 15/24 (62.5%) vs 2/21 (9.5%), $p<0.001$.

7.7.6 Leg shortening

Leg length shortening was measured in the AP pelvis radiographs and was less in the nail group at all time points:

- At 2 weeks: 5.1mm vs 9.8mm, $p=0.032$.
- At 4 weeks: 5.1mm vs 12.1mm, $p=0.004$.
- At 12 weeks: 6.8mm vs 12.2mm, $p=0.029$.

7.7.7 Fracture healing

Fracture healing was assessed by using the RUSH score (Figure 8).

The mean RUSH score was descriptively higher in the DHS group than in the nail group (24.5 vs 22.9, $p=0.277$) but this was not a statistically significant difference. Furthermore, higher proportion of patients in the DHS had RUSH score ≥ 18 (RUSH score < 18 is suggestive of non-union); 22/24 (91.7%) of the patients in the DHS group vs 16/21 (76.2%) of the patients in the nail group, but this was not a statistically significant difference.

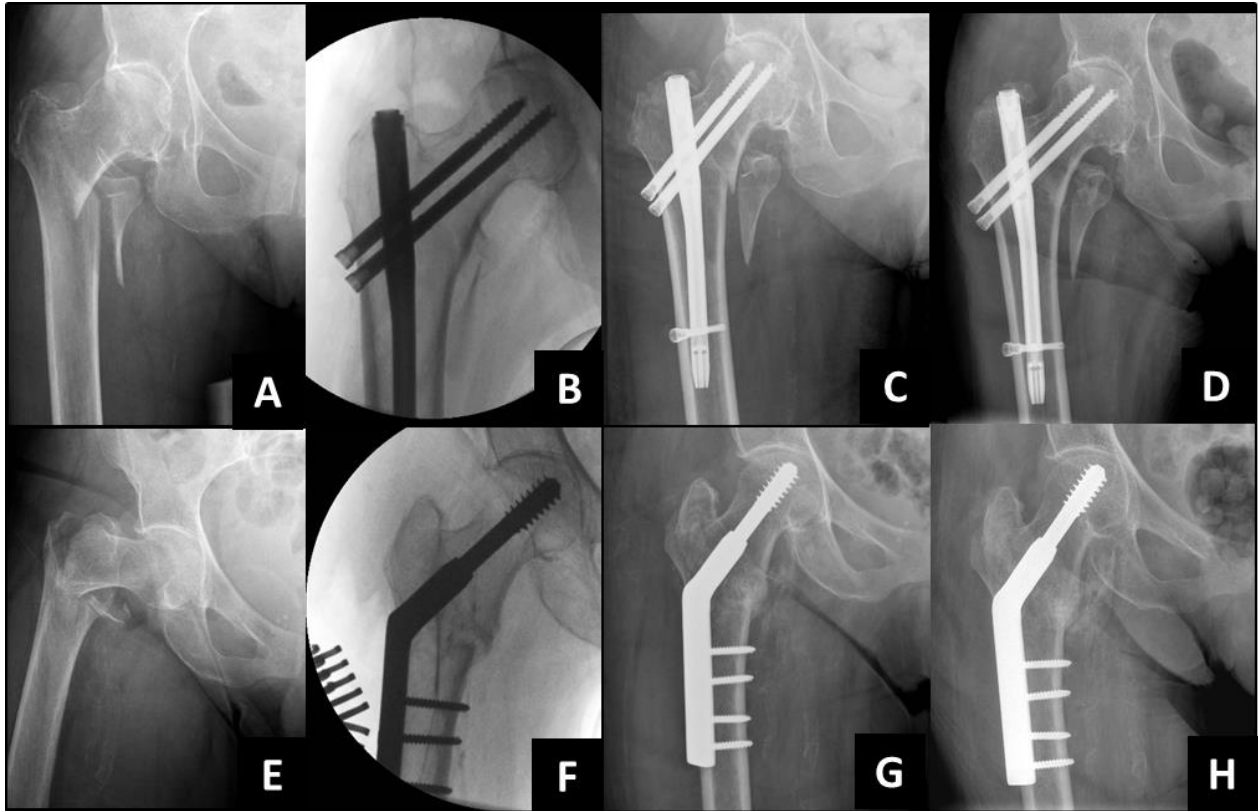


Figure 8: Assessment of fracture healing; Patient randomised in the nail group: A. Pre-operatively, B. Intraoperatively, C. At 2 weeks, D. At 12 weeks. Patient randomised in the DHS group: A. Pre-operatively, B. Intraoperatively, C. At 2 weeks and D. At 12 weeks.

Table 22: Radiographic results.

| Mean (SD) | Treatment received | | | p-value |
|--|--------------------|-------------|---|---------|
| | Nail | DHS | Difference (Nail-DHS) in means (95% CI), n | |
| Tip-apex distance, mm | 18.2 (6.8) | 14.9 (4.3) | 3.2 (0.1, 6.4), n=54 | 0.044 |
| Tip-apex distance: n/N (%) | | | | |
| >25mm | 4/26 (15.4) | 0/28 (0.0) | | 0.047 |
| <=25mm | 22/26 (84.6) | 28/28 (100) | | |
| <hr/> | | | | |
| Neck-shaft angle week 2, ° | 127.4 (6.6) | 133.6 (5.4) | -6.2 (-9.5, -2.8) | 0.001 |
| Neck-shaft angle week 4, ° | 126.5 (5.9) | 133.8 (6.2) | -7.4 (-10.8, -3.9) | <0.001 |
| Neck-shaft angle week 12, ° | 126.8 (7.6) | 133.6 (6.6) | -6.8 (-11.1, -2.4) | 0.003 |
| <hr/> | | | | |
| Neck-shaft angle difference week 12 vs 2, ° | -0.8 (3.6) | -0.1 (2.9) | 0.7 (-1.3, 2.7) | 0.490 |
| Neck-shaft angle change week 2 vs week 12 for Nail, ° | 0.8 (3.6) | | (-0.9, 2.6) | 0.332 |
| Neck-shaft angle change week 2 vs week 12 for DHS, ° | | 0.1 (2.9) | (-1.2, 1.4) | 0.918 |
| <hr/> | | | | |
| Proximal screw collapse week 4 vs 2, mm | 1.7 (2.1) | 2.3 (2.7) | -0.6 (-2.0, 0.8), n=47 | 0.371 |
| Proximal screw collapse week 12 vs 2, mm | 2.5 (3.8) | 3.7 (4.9) | -1.2 (-3.7, 1.3), n=45 | 0.349 |
| <hr/> | | | | |
| Neck collapse week 2, mm | 1.2 (2.2) | 9.5 (8.6) | -8.3 (-12.3, -4.3), n=42 | <0.01 |
| Neck collapse week 4, mm | 3.4 (4.0) | 10.6 (8.1) | -7.2 (-11.3, -3.1), n=42 | 0.001 |
| Neck collapse week 12, mm | 2.9 (3.5) | 12.2 (9.4) | -9.4 (-14.4, -4.7), n=37 | 0.001 |
| <hr/> | | | | |
| Medialisation week 2, mm | 2.6 (3.0) | 5.0 (3.2) | -2.4 (-4.2, -0.7), n=52 | 0.007 |
| Medialisation week 4, mm | 2.3 (2.1) | 5.8 (3.8) | -3.4 (-5.3, -1.6), n=49 | <0.001 |
| Medialisation week 12, mm | 2.7 (4.4) | 5.8 (3.8) | -3.1 (-5.6, -0.6), n=45 | 0.016 |
| <hr/> | | | | |
| Medialisation week 2: n/N (%) | | | | 0.003 |
| <5mm | 22/25(88.0) | 12/27(44.4) | | |
| >=5mm | 3/25 (12.0) | 15/27(55.6) | | |
| <hr/> | | | | |
| Medialisation week 4: n/N (%) | | | | 0.001 |
| <5mm | 20/23(87.0) | 10/26(38.5) | | |
| >=5mm | 3/23 (13.0) | 16/26(61.5) | | |
| <hr/> | | | | |
| Medialisation week 12: n/N (%) | | | | <0.001 |
| <5mm | 19/21(90.5) | 9/24 (37.5) | | |
| >=5mm | 2/21 (9.5) | 15/24(62.5) | | |

| | | | | |
|------------------------|--------------|--------------|--------------------------|-------|
| Shortening week 2, mm | 5.1 (5.7) | 9.8 (9.0) | -4.7 (-8.9, -0.4), n=50 | 0.032 |
| Shortening week 4, mm | 5.1 (6.0) | 12.1 (9.5) | -7 (-11.5, -2.4), n=48 | 0.004 |
| Shortening week 12, mm | 6.8 (7.0) | 12.2 (8.6) | -5.4 (-10.2, -0.6), n=44 | 0.029 |
| RUSH score | 22.9 (5.7) | 24.5 (4.4) | -1.7 (-4.8, 1.4), n=45 | 0.277 |
| RUSH score: n/N (%) | | | | |
| <18 | 5/21 (23.8) | 2/24 (8.3) | | 0.153 |
| >=18 | 16/21 (76.2) | 22/24 (91.7) | | |

7.8 Associations

7.8.1 Associations between patient factors and TUG test

As a guideline rho between 0.3 and 0.5 indicates moderate association and rho>0.5 indicates strong association between the variables.

Age did not tend to be associated with number of TUG trial completed but it was associated with TUG time. ASA score was associated with both number of trials and TUG time, particularly at 2 and 4 weeks. Within patients with ASA=2, age was associated with TUG time, but the age association was weaker for ASA=3 or 4.

Table 23: Associations between age and ASA score and TUG test.

| | Week 2 | Week 4 | Week 12 |
|--|------------------------|------------------------|-----------------------|
| Number of TUG trials completed vs.: | | | |
| Age | rho=-0.10, n=34 | rho=-0.09, n=34 | rho=0.02, n=32 |
| ASA score | rho=-0.53, n=34 | rho=-0.32, n=34 | rho=-0.25, n=32 |
| Age, if ASA=2 | rho=-0.16, n=15 | rho=0.15, n=15 | rho=0.14, n=16 |
| Age, if ASA=3 or 4 | rho=-0.25, n=19 | rho=-0.30, n=19 | rho=-0.02, n=16 |
| Best TUG time vs.: | | | |
| Age | rho=0.27, n=26 | rho=0.28, n=29 | rho=0.35, n=30 |
| ASA score | rho=0.34, n=26 | rho=0.41, n=29 | rho=0.28, n=30 |
| Age, if ASA=2 | rho=0.53, n=14 | rho=0.61, n=13 | rho=0.42, n=16 |
| Age, if ASA=3 or 4 | rho=0.30, n=12 | rho=0.10, n=16 | rho=0.25, n=14 |

7.8.2 Association between radiographic outcomes and patient reported outcomes

To assess whether radiographic outcomes were associated with functional mobility or quality of life we assessed the correlation between radiographic variables (neck collapse, medialisation and leg shortening) and PROMs (LEM, LHS, DEMQOL, DEMQOL-carer and TUG score).

Better function (LEM and LHS) was negatively moderately correlated with leg shortening at 12 weeks ($\rho=-0.47$, $p=0.006$ and $\rho=-0.44$, $p=0.011$ respectively). Moreover, DEMQOL-cares was strongly negatively associated with neck collapse at 12 weeks ($\rho=-0.68$, $p=0.046$).

There were no other associations between PROMs and the rest of radiological variables (Table 24).

Table 24: Associations between PROMs and radiographic variables.

| | Week 2 | Week 4 | Week 12 |
|---------------------|---------------------|---------------------|--|
| LEM score | | | |
| Neck collapse | $\rho=-0.19$, n=30 | $\rho=-0.26$, n=30 | $\rho=-0.07$, n=27 |
| Medialisation | $\rho=-0.07$, n=37 | $\rho=-0.05$, n=36 | $\rho=-0.04$, n=34 |
| Leg shortening | $\rho=-0.06$, n=35 | $\rho=-0.13$, n=35 | $\rho=-0.47^{**}$, n=33 |
| LHS | | | |
| Neck collapse | $\rho=-0.07$, n=30 | $\rho=-0.11$, n=30 | $\rho=0.03$, n=27 |
| Medialisation | $\rho=-0.14$, n=37 | $\rho=-0.12$, n=36 | $\rho=-0.13$, n=34 |
| Leg shortening | $\rho=-0.17$, n=35 | $\rho=-0.06$, n=35 | $\rho=-0.44^*$, n=33 |
| DEMQOL | | | |
| Neck collapse | $\rho=-0.39$, n=10 | $\rho=-0.19$, n=10 | $\rho=-0.62$, n=8 |
| Medialisation | $\rho=-0.17$, n=13 | $\rho=0.01$, n=12 | $\rho=-0.35$, n=10 |
| Leg shortening | $\rho=0.01$, n=13 | $\rho=-0.04$, n=12 | $\rho=-0.46$, n=10 |
| DEMQOL-carer | | | |
| Neck collapse | $\rho=-0.36$, n=12 | $\rho=-0.27$, n=11 | $\rho=-0.68^*$, n=9 |
| Medialisation | $\rho=-0.18$, n=15 | $\rho=0.22$, n=13 | $\rho=0.17$, n=11 |
| Leg shortening | $\rho=0.03$, n=15 | $\rho=0.30$, n=13 | $\rho=-0.05$, n=11 |
| TUG time | | | |
| Neck collapse | $\rho=-0.05$, n=28 | $\rho=0.01$, n=34 | $\rho=-0.05$, n=31 |
| Medialisation | $\rho=0.24$, n=33 | $\rho=-0.06$, n=42 | $\rho=-0.01$, n=39 |
| Leg shortening | $\rho=-0.05$, n=32 | $\rho=0.04$, n=41 | $\rho=0.03$, n=38 |

* $p<0.05$, ** $p<0.01$

Moreover, in an attempt to assess whether malunited fractures were associated with worse PROMS, we compared PROMS (i.e. LEM, LHS, DEMQOL, DEMQOL-carer and TUG test) between patients with signs of malunion and patients without.

Malunion was defined as >5mm of medialisation (112), more than 1cm of leg shortening (131) or change in the neck shaft angle >5° at week 12.

There was a similar proportion of patients with malunited fractures in the nail and DHS group; there were 10 patients (10/21, 47.6%) in the nail group and 18 patients (18/24, 75%) in the DHS group ($p=0.059$).

Patients with malunited fractures had significantly lower functional levels as these were measured with the LEM and the London Handicap Scale (Table 25). The TUG times were also descriptively lower in patients with non-malunited fractures but the difference between the groups was not statistically significant.

Table 25: Comparison of PROMS between malunited and non-malunited fractures at week 12.

| | No Malunion | Malunion | Mean difference (CI 95%) | p-value |
|---------------------|-------------|-----------|--------------------------|---------|
| LEM | 70.4±16.5 | 50.0±23.8 | 21.4 (35.8, 7.0) | 0.005 |
| LHS | 0.81±0.1 | 0.66±0.1 | 0.2 (0.2, 0.1) | 0.004 |
| DEMQOL | 94.7±11.8 | 74.8±18.6 | 19.9 (47.6, -7.7) | 0.121 |
| DEMQOL-carer | 90.2±17.3 | 93.8±23.9 | -3.6 (-31.6, 24.5) | 0.788 |
| TUG test | 37.5±18 | 53.6±57.8 | 16.1 (-14.3, 46.5) | 0.289 |

7.8.3 Associations between LOS and PROMS

There was a degree of moderate positive association between the LOS and the TUG test at week 4 ($\rho=0.39$, $p=0.01$). There was not any other significant association between the LOS and the PROMS.

Table 26: Associations between LOS and PROMS.

| LOS | TUG2 | TUG4 | TUG12 | LEM2 | LEM4 | LEM12 | DEMQOL2 | DEMQOL4 | DEMQOL12 |
|----------------|-------|-------------|-------|-------|-------|-------|---------|---------|----------|
| rho | 0.05 | 0.39 | 0.24 | -0.22 | -.032 | -0.23 | 0.11 | 0.34 | 0.02 |
| p-value | 0.788 | 0.010 | 0.149 | 0.199 | 0.056 | 0.166 | 0.732 | 0.284 | 0.954 |
| n | 33 | 42 | 39 | 37 | 37 | 37 | 13 | 12 | 10 |

7.8.4 Associations between LOS and radiographic variables

There was no significant association between LOS and radiographic variables (Table 27).

Table 27: Associations between LOS and radiographic variables

| LOS | Neck collapse2 | Neck collapse4 | Neck collapse12 | LLD2 | LLD4 | LLD1 | Medial 2 | Medial 4 | Medial 12 |
|----------------------|-------------------|-------------------|--------------------|-------|-------|-------|----------|----------|-----------|
| rho | -0.15 | -0.07 | -0.07 | 0.03 | -0.12 | -0.04 | -0.08 | -0.06 | -0.08 |
| p-value | 0.362 | 0.644 | 0.690 | 0.860 | 0.423 | 0.786 | 0.602 | 0.689 | 0.593 |
| n | 41 | 41 | 37 | 49 | 48 | 44 | 51 | 49 | 45 |
| Medial=medialisation | | | | | | | | | |

7.9 Additional confidence intervals for key outcomes

To supplement the results for key outcomes, a range of confidence intervals (75%, 80%, 85%, 90%, 95%) have been calculated, to indicate whether proof-of-concept was obtained at a lower level of confidence. These were calculated for days until ready for discharge, in-patient length of stay, pain NRS at weeks 2, 4 and 12, and morphine requirements (Table 28). Comparisons have been made by treatment received.

For days until ready for discharge there was preliminary evidence of a difference in favour of nail at the 80% level of confidence, but again this was largely due to the patients with AMTS<8, for whom there was evidence at all levels of confidence from 75-95%.

There was no preliminary evidence of a difference in in-patient length of stay at 75-95% confidence.

There was preliminary evidence of a difference in pain NRS in favour of nail at 90% confidence at weeks 2 and 4. However, there was also preliminary evidence of a difference in favour of DHS at 85% confidence at week 12.

For morphine equivalent dose there was no preliminary evidence of a difference in patients with AMTS>=8. However, for patients with AMTS<8 there was evidence in favour of nail at 80% confidence.

Table 28: Unplanned additional confidence intervals for key variables.

| Variable: CI | Difference (DHS-Nail) (95% CI) | | |
|--|--------------------------------|---------------------|---------------------|
| | All patients | AMTS \geq 8 | AMTS $<$ 8 |
| Days until ready: Ratio | n=54 | n=36 | n=18 |
| 75% CI | 1.2 (1.0, 1.5) | 1.0 (0.8, 1.3) | 1.9 (1.4, 2.6) |
| 80% CI | 1.2 (1.0, 1.5) | 1.0 (0.7, 1.3) | 1.9 (1.3, 2.7) |
| 85% CI | 1.2 (0.9, 1.6) | 1.0 (0.7, 1.4) | 1.9 (1.3, 2.8) |
| 90% CI | 1.2 (0.9, 1.6) | 1.0 (0.7, 1.4) | 1.9 (1.2, 3.0) |
| 95% CI | 1.2 (0.9, 1.7) | 1.0 (0.6, 1.5) | 1.9 (1.1, 3.3) |
| In-patient LOS, days: Ratio | n=53 | n=36 | n=17 |
| 75% CI | 0.8 (0.7, 1.0) | 0.9 (0.8, 1.1) | 0.8 (0.6, 1.0) |
| 80% CI | 0.8 (0.7, 1.0) | 0.9 (0.7, 1.1) | 0.8 (0.6, 1.0) |
| 85% CI | 0.8 (0.7, 1.0) | 0.9 (0.7, 1.1) | 0.8 (0.6, 1.0) |
| 90% CI | 0.8 (0.7, 1.0) | 0.9 (0.7, 1.1) | 0.8 (0.5, 1.1) |
| 95% CI | 0.8 (0.7, 1.1) | 0.9 (0.7, 1.2) | 0.8 (0.5, 1.1) |
| Pain NRS (0-10) week 2: Median difference | n=40 | n=34 | |
| 75% CI | 2.0 (0.9, 3.1) | 2.0 (0.8, 3.2) | |
| 80% CI | 2.0 (0.8, 3.2) | 2.0 (0.6, 3.4) | |
| 85% CI | 2.0 (0.6, 3.4) | 2.0 (0.4, 3.6) | |
| 90% CI | 2.0 (0.4, 3.6) | 2.0 (0.2, 3.8) | |
| 95% CI | 2.0 (0.1, 3.9) | 2.0 (-0.1, 4.1) | |
| Pain NRS (0-10) week 4: Median difference | n=39 | n=34 | |
| 75% CI | 2.0 (0.8, 3.2) | 2.0 (0.6, 3.4) | |
| 80% CI | 2.0 (0.6, 3.4) | 2.0 (0.5, 3.5) | |
| 85% CI | 2.0 (0.5, 3.5) | 2.0 (0.3, 3.7) | |
| 90% CI | 2.0 (0.3, 3.7) | 2.0 (0.1, 3.9) | |
| 95% CI | 2.0 (-0.1, 4.1) | 2.0 (-0.3, 4.3) | |
| Pain NRS (0-10) week 12: Median difference | n=39 | n=35 | |
| 75% CI | -2.0 (-3.4, -0.6) | -2.0 (-3.6, -0.4) | |
| 80% CI | -2.0 (-3.6, -0.4) | -2.0 (-3.8, -0.2) | |
| 85% CI | -2.0 (-3.8, -0.2) | -2.0 (-4.0, 0.0) | |
| 90% CI | -2.0 (-4.0, 0.0) | -2.0 (-4.3, 0.3) | |
| 95% CI | -2.0 (-4.4, 0.4) | -2.0 (-4.8, 0.8) | |
| Morphine equivalent dose, mg: Median difference | n=52 | n=34 | n=18 |
| 75% CI | 32.0 (-4.0, 68.0) | 22.5 (-29.2, 74.2) | 68.5 (12.9, 124.1) |
| 80% CI | 32.0 (-8.1, 72.1) | 22.5 (-35.1, 80.1) | 68.5 (6.6, 130.4) |
| 85% CI | 32.0 (-13.0, 77.0) | 22.5 (-42.2, 87.2) | 68.5 (-1.0, 138.0) |
| 90% CI | 32.0 (-19.4, 83.4) | 22.5 (-51.4, 96.4) | 68.5 (-11.0, 148.0) |
| 95% CI | 32.0 (-29.3, 93.3) | 22.5 (-65.5, 110.5) | 68.5 (-26.2, 163.2) |

7.10 Power analysis for a full trial

For the purposes of this feasibility study, we used the TUG test as the primary assessment measure. More precisely, we hypothesized that all patients would be able to perform this test at week 4 and the results of the test between the groups would reveal a clinically meaningful preliminary proof of concept difference.

However, the results of this study, have shown that:

- Only 42/50 patients (84%) who attended week 4 follow-up visit were able to perform the test at least once.
- Four patients (all with AMTS<8) had died before this time point and overall 50/60 patients (83.3%) completed week 4 visit (high attrition).
- There was high variability in the TUG time results (range 13sec – 381sec); this makes it difficult to detect a difference between the groups.

For all these reasons we concluded that the TUG test is not a suitable efficacy measure for such a trial.

The ideal primary efficacy measure for this elderly population with hip fractures, would be a variable that can be assessed early and will not be influenced by the high level of attrition at later time points. Also, this variable should be easy to measure in patients with and without dementia. For example, the TUG test was proved to be a difficult physical assessment test and some patients with advanced dementia were unable to perform it at all. Similarly, patient-reported outcome scores are good for cognitive intact patients but patients with dementia still struggled to complete them, as it happened with the DEMQOL in this trial.

In conclusion, except for the radiographic variables, none of the PROMs or the TUG test seemed to differ significantly between the 2 groups in this study. The radiographic variables differed significantly between the groups, but they did not seem to affect functional mobility. Therefore, no power analysis for a future full-scale trial was performed since the TUG test was not a suitable measure for this patient group and the other efficacy variables used in this study did not differ significantly between the groups.

7.11 Retrospective review of patients with cognitive impairment – LGI cohort

To assess the mortality and the incidence of complications in patients with cognitive impairment, a retrospective study including all the patients with hip fractures presented at Leeds General Infirmary between January 2018 and September 2020 was carried out. This time scale represents the same time period as the main trial was run.

A search in the national hip fracture database was conducted and all patients with AO/OTA 31 A1 and A2 fractures were identified. Only patients with AMTS<8 were included. Patients with type A3 fractures were excluded as this fracture pattern differs to types A1 and A2 and patients with A3 fractures can only be treated with a long intramedullary nail.

Data collection included date of death, medical and surgical complications.

Additionally, the main study showed that there was descriptive difference between the nail and the DHS group in the length of hospital stay (24.5 vs 21.4 days) and the days till ready for discharge (8.6 vs 10.5 days), especially in the AMTS<8 group (Table 11). Moreover, while patients with AMTS<8 treated with a DHS had shorter LOS than patients treated with a nail (24.2 vs 29.7 days), patients treated with a nail had considerably less 'days till ready for discharge' (9.2 vs 17.6 days). It should be emphasised that the compared groups for these results were very small in size (8-9 participants per group). In order to assess this finding further, data for LOS was also collected.

In total, 524 patients with types A1 and A2 hip fractures were identified, and 213 had AMTS <8 and were included in the study. The average age was 87.5 ± 7.6 years.

There were 180 patients (85.5%) who were treated with a DHS (Zimmer-Biomet) and 33 patients (15.5%) who were treated with a nail (Affixus, Zimmer-Biomet, all but one of the patients had a long nail).

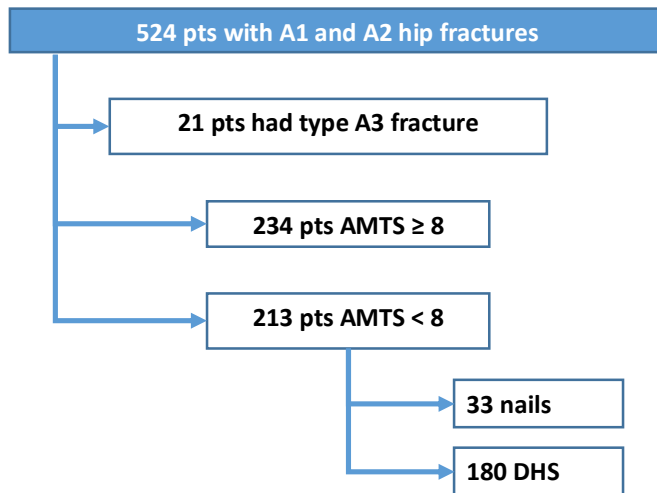


Figure 9: LGI-cohort patient flowchart

7.11.1 Mortality rates

Overall, in-hospital mortality rate was 11.7% (25/213), 30-day mortality was 12.7% (27/213) and 1-year mortality was 47.4% (101/213).

Split per treatment received, in-hospital and 30-day mortality was significantly higher in patients treated with a nail than patients treated with a DHS (Table 29). Although mortality appeared to be higher in patients treated with a nail at 1-year, this was not a statistically significant difference.

Table 29: Mortality as per treatment group (LGI cohort)

| n/N (%) | Nail | DHS | p-value |
|--------------------|---------------|----------------|---------|
| In-hospital | 8/33 (24.2%) | 17/180 (9.4%) | 0.015 |
| 30-day | 8/33 (24.2%) | 19/180 (10.6%) | 0.030 |
| 1-year | 20/33 (60.6%) | 81/180 (45.0%) | 0.099 |

7.11.2 Complications

Overall, 84 patients (39.4%) developed at least one complication (Table 30). The total number of complications recorded was 101.

Medical complications included 51 infections (i.e. lower respiratory tract infection, urinary tract infection, otitis externa), 10 skin complications (i.e. pressure sores), 10 respiratory disorders (i.e. aspiration pneumonia, pulmonary embolism), 9 gastrointestinal disorders (i.e. haemorrhage, cholangitis, cholecystitis, bowel perforation and bowel ischaemia), 8 cardiac events (i.e. arrhythmias and acute coronary syndrome), 3 neurological disorders (i.e. stroke, seizure), 1 renal disorder (i.e. end stage renal failure), 1 metabolic disorder (i.e. hypoglycaemia) and 1 vascular disorder (i.e. deep vein thrombosis).

There were 7 surgery related complications: There was 1 cut-out in the nail group and 6 surgery-related complications in the DHS group (2 wound dehiscence, 2 peri-implant fractures, and 1 deep and 1 superficial wound infection).

Although there was a higher number of medical and surgical complications in the DHS groups, similar percentage of patients in both groups had medical or surgical related complications.

However, when comparing all complications in total, there were significantly more patients with a complication treated with a nail than patients treated with a DHS (54.5% vs 36.7%, $p=0.044$).

Table 30: Complications in patients with cognitive impairment (LGI cohort).

| | Nail | DHS | p-value |
|--------------------------------|---------------|----------------|----------------|
| Medical | | | |
| Patients affected | 17/33 (51.5%) | 64/180 (35.6%) | 0.083 |
| Number of complications | 19 | 75 | |
| Surgical | | | |
| Patients affected | 1/33 (3.0%) | 6/180 (3.3%) | 0.928 |
| Number of complications | 1 | 6 | |
| Total | | | |
| Patients affected | 18/33 (54.5%) | 66/180 (36.7%) | 0.044 |
| Number of complications | 20 | 81 | |

7.11.3 Length of stay

The average length of stay in this cohort was 21.6 ± 11.7 days.

Split per treatment group, there was no significant difference between patients treated with a nail and a DHS (24.3 ± 11.5 vs 21.2 ± 11.7 , $p=0.209$).

Interestingly, the mean LOS in this cohort was smaller than the mean LOS of the main trial.

7.12 Optimisation of technique of measuring screw collapse

Because the degree of the lag screw visible on plain radiographs depends on the degree of rotation of the leg, a trigonometry study was recommended. The aim of the study would be to predict the length of the cephalic screw taking into account the degree of rotation of the hip. However, the trigonometry rules did not apply on the measurements from the radiographs. For example, the measurements of the length of the screw and the length of the nail/plate on x-ray viewing software did not agree with the measured angles (i.e. trying to calculate the sine, cosine or tangent of a measured angle did not agree with the trigonometric values for that given angle). This was probably because the radiographs produce a 2D image of a 3D structure and trigonometric functions apply for triangles in the same dimension (and not in 3-dimension shapes).

To overcome the above issue, an opinion of a specialist MSK radiologist (Dr James Rankine) from Leeds General Infirmary was sought, who advised that the best way to estimate the length of the screw would be by expressing it as a proportion of the whole length of the screw (i.e. the rate of the measured collapse towards the measured full length of the screw), (Figure 9). Since the whole length of the screw is known, by multiplying the above rate with the true length of the screw, the true collapse could be best estimated. Any discrepancy of the measured collapse due to the rotation of the leg would be proportional to any discrepancy of the measured length of the screw and since that rate is multiplied with the true length of the screw, the estimate would be as accurate as possible.

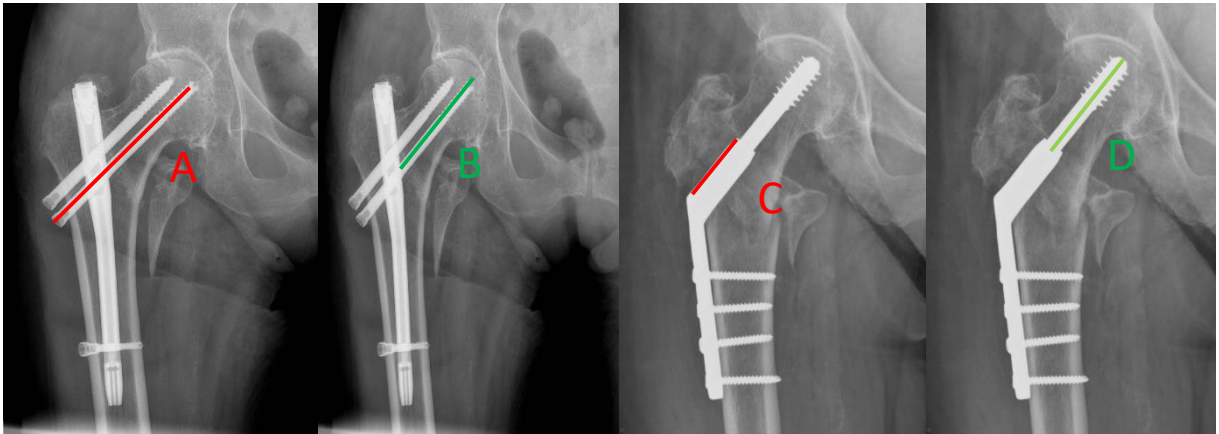


Figure 10: Measuring technique of neck collapse: A: length of proximal locking screw length, B: neck collapse in the nail group, C: length of barrel, and D: neck collapse in the DHS group.

This measuring technique was applicable to all patients with a nail. However, in some patients with a DHS, the 'lag' screw was within the barrel of the plate and therefore it was not possible to measure its length accurately. For this reason, the length of the barrel was used as a reference in all patients with a DHS and neck collapsed was measured in reference to the measured and true length of the barrel.

Re-measuring of neck collapse

Neck collapse at week 4 was significantly higher (1.6 vs 3.4mm, $p=0.016$) in the DHS group (Table 31). However, the difference was not statistically significant at 12 weeks (2.4 vs 4.5, 95% CI: -4.6, 0.3, $p=0.089$).

Measuring neck collapse with this technique resulted to similar measurements for the nail group (Table 22), but higher measurements for the DHS group.

Table 31: Neck collapse using revised technique.

| | Nail | DHS | Mean difference (95%CI) | P-value |
|-----------------------------|---------|---------|-------------------------|---------|
| Neck collapse week 2-4, mm | 1.6±2.0 | 3.4±2.6 | -1.7 (-3.1, -0.3) n=47 | 0.016 |
| Neck collapse week 2-12, mm | 2.4±2.8 | 4.5±5.0 | -2.1 (-4.6, 0.3) n=43 | 0.089 |

7.13 Efficacy conclusions

- Patients treated with a nail reported significantly lower levels of pain at 2 weeks than patients treated with a DHS. Pain levels were similar between the groups at 2 and 12 weeks.
- Patients treated with a nail had better radiographic outcomes (neck collapse, leg length shortening, and medialisation); the mean TAD distance was significantly lower in the DHS group.
- Time till ready for discharge was shorter for patients who received a nail than patients who received a DHS in patients with cognitive impairment. However, this was not translated to shorter overall hospital stay or it was not associated with better mobility. It is noteworthy that time till ready for discharge is a difficult variable to define and to measure because it depends on the judgement of the physiotherapy team. If this variable is going to be used in a future study, clear criteria which will define when a patient is ready for discharge will need to be determined.
- There was no significant difference in the TUG times between the groups. There was no difference in the ability of patients to perform the TUG test between the nail and the DHS group. However, at 2 weeks, it was significantly more likely for patients without cognitive impairment to be able to perform the test than patients with cognitive impairment (there was no difference at 4 and 12 weeks).
- There was no difference in blood loss and blood transfusion requirements between the groups; however, a future study should include a method to report the overall blood loss rather than blood loss separately from the suction and from the weight of surgical swabs.
- Patients who were treated with a DHS had descriptively higher average opioid requirements within the first 2 weeks than patients who received a nail; a future study with a bigger sample size will determine whether this is a significant difference between the groups.
- Functional outcome scores (i.e. LEM and DEMQOL) did not differ to a clinically meaningful extent.
- There was a moderate association between the LEM and LHS and leg shortening; also, there was strong association between neck collapse and DEMQOL-carer.
- Patients with non-malunited fractures had significantly better functional scores (assessed with the LEM and LHS instruments) compared to patients with malunited fractures.
- There was moderate association between length of stay and TUG times at week 4.

Chapter 8

Safety Evaluation

8.1 Brief summary of adverse events

All adverse events were reported according to Common Terminology Criteria for Adverse Events (CTCAE). Overall, 28 adverse events were recorded in 26 patients (Table 32). Most of the adverse events were infection related (7 episodes) or respiratory system related (4 episodes). There were 2 re-admissions. One patient was re-admitted after week-4 follow-up after a fall. An x-ray was performed which did not reveal any new injuries. Patient stayed overnight and they were discharged back to their own home the day after. The 2nd patient was readmitted also after week-4 review due to new onset of pain to their hip. They did not have a history of trauma. They had an X-ray which revealed an undisplaced peri-prosthetic fracture. They were treated non-operatively and after 5 days they returned to their usual place of residence.

The severity of the adverse events is shown on Table 32. Overall, there were 6 deaths. None of them was related to this trial's interventions. The cause of death was always related to the patients' comorbidities (stroke, ischemic heart event, frailty etc.). All deaths were reported to the sponsor and no further action was required. Four patients developed life threatening adverse events (acute coronary syndrome, respiratory failure, pulmonary embolism). Apart from the patient who developed acute coronary syndrome, all patients made full recovery. The patient with the acute coronary syndrome did not recover and died 4 days after the onset of the event.

Except of one, all adverse events were unrelated to the study. The only adverse event which was related to the study was the patient who sustained an undisplaced peri-prosthetic fracture just below the distal cephalic screw in the nail group.

Table 32: Adverse events.

| AMTS | Randomised group | Severity | Description | SAE |
|------|------------------|----------|--|-----|
| <8 | DHS | 3 | Vaginal haemorrhage | No |
| <8 | DHS | 2 | Phlebitis | No |
| <8 | Nail | 4 | Thromboembolic event | Yes |
| >=8 | Nail | 1 | Social circumstances: failed discharge | No |
| <8 | DHS | 5 | Death NOS | Yes |
| <8 | Nail | 5 | Stroke | Yes |
| <8 | Nail | 5 | Death NOS | Yes |
| >=8 | Nail | 3 | Scrotal infection | No |
| >=8 | Nail | 3 | Right ventricular dysfunction | No |
| <8 | Nail | 1 | Eye infection | No |
| <8 | DHS | 3 | Kidney infection | No |
| <8 | DHS | 3 | Lung infection | No |
| <8 | DHS | 3 | Aspiration pneumonia | No |
| >=8 | Nail | 4 | Respiratory failure | Yes |
| >=8 | Nail | 4 | Thromboembolic event | Yes |
| >=8 | Nail | 2 | Lung infection | No |
| >=8 | DHS | 3 | Upper gastrointestinal haemorrhage | Yes |
| >=8 | DHS | 2 | Vaginal haemorrhage | No |
| <8 | DHS | 5 | Death NOS | Yes |
| <8 | Nail | 2 | Fracture (right patella) | No |
| >=8 | DHS | 3 | Lung infection | No |
| <8 | DHS | 1 | Haematuria | No |
| <8 | DHS | 2 | Bladder infection | No |
| <8 | DHS | 3 | Bladder infection | No |
| <8 | Nail | 4 | Acute coronary syndrome | Yes |
| <8 | Nail | 5 | Death NOS | Yes |
| >=8 | Nail | 3 | Fracture (periprosthetic) | Yes |
| <8 | Nail | 5 | Lung infection | Yes |

SAE: Significant adverse event

8.2 Narratives of deaths and other serious adverse events

Deaths

There were 6 deaths in total:

Patient 32: This patient (91 years old female) was randomised to the DHS group and received a DHS. She had an ASA score of 3 and she was known to have atrial fibrillation. Postoperatively she developed flutter, and this slowed down her recovery. In week-2 follow-up she was still bedbound due to tachycardia (flutter). In week 4 follow-up she was still inpatient, and she was unable to perform the TUG test. The overall hospital stay was 28 days. She had been admitted from her own home and was discharged to a rehabilitation unit. Twenty-two days after discharge she became unwell, and she was admitted in the hospital. She was treated for urosepsis. Due to her comorbidities and overall frailty, she received palliative care. Due to bad prognosis, she was transferred to a nursing home where she died a couple of days later.

The cause of death was reported as pneumonia and it was unrelated to the treatment she had received for the hip fracture. The death was reported to the sponsor and no further action was required.

Patient 33: This patient (86 years old female) was randomised in the nail group. She was admitted with acute onset confusion. She was reviewed by the medical team on day 3, and she was found to have a stroke which hadn't been diagnosed on admission. She had an ASA score of 4 (atrial fibrillation, chronic obstructive pulmonary disease, ischemic heart disease, previous stroke with upper limb residual weakness, cognitive impairment, pernicious anaemia, Crohn's disease and hypertension). After the operation she was very drowsy and unresponsive. Due to frailty, she was started on end of life care. She died 7 days after surgery. The cause of death was documented as stroke and atrial fibrillation.

Her death was not related to the hip operation, it was reported to the sponsor and no further action was taken.

Patient 43: This patient (87 years old female) was randomised to the nail group and had an uneventful operation. She had an ASA score of 4 (cognitive impairment, hyperthyroidism, atrial fibrillation, previous stroke, and diverticular disease). She recovered well from surgery. She attended week 2 follow-up as planned. However due to cognitive impairment she was unable to follow any instructions or answer any questions and therefore she was unable to perform the TUG test or complete the questionnaires. While in hospital and awaiting discharge to a nursing home, she passed away quietly.

Her death was attributed to old age and was unrelated to the operation for the hip fracture. It was reported to the sponsor and no further action was taken.

Patient 79: This patient (92 years old male) was randomised to a DHS and had an uneventful operation. He had an ASA score of 3 (transient cell carcinoma of the bladder, an asymptomatic abdominal aortic aneurysm, diabetes mellitus and cerebrovascular disease). After the operation he became unwell, and he was treated for hospital acquired pneumonia. He gradually deteriorated further, and he died on day 4 from surgery.

His death was due to pneumonia, and it was unrelated to the operation he had. The death was reported to the sponsor and no further action was taken.

Patient 141: This patient (90 years old female) was randomised to a nail and had an uncomplicated operation. She had an ASA score of 3 (cognitive impairment, hypertension, and diet-controlled diabetes mellitus). On admission she received treatment for a lower respiratory tract infection. After the operation she was admitted in the high dependency unit. On further testing, she was found to have myocardial infraction. Her condition deteriorated further, and she died on day 7.

Her death was unrelated to the operation of the hip fracture, and it was reported to the sponsor. No further action was required.

Patient 144: This patient (85 years old female) was randomised to a nail and had an uncomplicated operation. She had an ASA score of 3 (cognitive impairment, chronic kidney disease, a previous stroke and hypertension). After the operation she was found to have elevated troponin, but a myocardial infraction was not confirmed. Overall, she stayed in the hospital for 21 days and eventually she was discharged to her pre-injury residential place which was a nursing home. She attended week-2 and week-4 follow-up visits. Fifteen days after the week-4 follow-up review, she was admitted in the hospital due to community acquired pneumonia. Two days later she died.

Their death was unrelated to the operation for the hip fracture, and it was reported to the sponsor. No further action was required.

Other serious adverse events

Overall, there were 12 significant adverse events (SAEs) in 10 patients.

Patient 32 (death), pt 33 (stroke), pt 43 (death), pt 79 (death), pt 141 (acute coronary syndrome and death), and pt 144 (lung infection) have been described above.

Patient 23: This patient (95 years old female) was randomised to a nail but received a DHS. She had an uneventful recovery, and she was discharged to a rehabilitation care home 20 days after surgery. She had an ASA score of 3 (cognitive impairment, hypertension, ischemic heart disease and ulcerative colitis). She attended week-2 follow-up visit and she was able to complete the TUG test and all the questionnaires. Just before week-4 visit, patient's consultee withdrew consent because travelling to the hospital was too distressful and inconvenient for the patient. A week later, she was admitted to the hospital under the medical team for chest pain. She was found to have pulmonary embolism and she received appropriate treatment. She stayed in the hospital for 1 night and she was discharged back to her own residence. She recovered fully from this event.

Thromboembolic events are recognized complications following hip fractures. Hip surgery (with a DHS) is not believed to directly cause thromboembolic events, but instead early surgery is believed to reduce the risk of this complication in patients with hip fractures.

Patient 57: This patient (70 years old female) was randomised to a nail. She had an ASA score of 4 (atrial fibrillation, asthma, hypertension, diabetes mellitus type 2, and cor pulmonale with right ventricular systolic impairment). On admission she was found to have community acquired pneumonia and she received suitable treatment. Surgery had to be delayed for two days until her medical condition had improved. One day after surgery she developed respiratory failure and she received cardiopulmonary resuscitation. She was admitted in the high dependency unit, and she received supportive treatment. Further imaging 10 days later revealed a left lower lobe segmental pulmonary embolism which was treated with suitable anticoagulant drugs. Following a 36-day hospital stay she was discharged to a rehabilitation care home. Patient attended all 3 follow-up visits and completed the trial.

The respiratory failure and the thromboembolic event were unrelated to the treatment she received for the hip fracture. Both are recognized complications following hip fractures and are more common in people with pre-existing severe cardiopulmonary comorbidities.

Patient 68: This patient (83 years old female) was randomised to a DHS. She had an ASA score of 3 (atrial fibrillation, hypertension, and paroxysmal supraventricular tachycardia). She had an uncomplicated

recovery. She was discharged to a rehabilitation care home 15 days after the operation. She attended week-2 follow-up review without any problems. Seven days later, she was admitted under the medical team due to upper gastrointestinal haemorrhage. She had gastroscopy which revealed duodenal ulcers. She stayed in the hospital for overall 19 days and finally she was discharged back to the rehabilitation care home. She made a full recovery. She attended week-4 and week-12 follow-up visits as planned and she completed the study.

Upper gastrointestinal bleeding is a significant adverse event however it was not related to the study, and it was not reported to the sponsor.

Patient 142: This patient (84 years old female) was randomised to a nail. She had an uncomplicated operation. She had an ASA score of 3 (essential tremor and osteoporosis). She had an uncomplicated recovery, and she was discharged to her own home after a 20-day hospital stay. She attended week-2 and week-4 follow-up visits as planned. Five days after week-4 review, she woke up with worsening hip pain and a subsequent x-ray revealed a fracture line (undisplaced fracture) just distally to the distal cephalic screw. This injury was treated non-operatively. She stayed in the short stay ward for 5 days and she was discharged back to her own home. By week-12 review she had fully recovered.

This adverse event was deemed severe because the patient presented to the hospital. It was related to the intervention. However, no specific cause for this complication was identified.

Other significant adverse events

Patient 57: The medical complications for this patient have already been described above. She remained under follow-up after completion of the trial visits because of impending metalwork failure. During that time, she remained unable to mobilize. Radiographs revealed failure of the nail (varus collapse and screw cut through). One year after the index procedure she returned to theatres for removal of the proximal femoral screw under local anaesthetic. Due to her severe comorbidities and the high risk of general anaesthesia, she was not fit for any further surgery. Following removal of the screw, patient returned to her own residence, but her mobility did not improve. She continued to deteriorate, and she required multiple admissions to the hospital due to respiratory tract infections. She died 2 months after removal of the proximal hip screw.

8.3 Analysis and discussion of deaths and other serious adverse events

Overall, only one complication was related to the surgical intervention. This was the patient who sustained a peri-prosthetic fracture 5 weeks after their operation. No cause of this complication was identified.

Except for the peri-prosthetic fracture described above, no other surgery-related complication was observed during the 12-week follow-up period. The main reason for this was most likely the small sample size and the short follow-up period. Moreover, all procedures were performed by experienced trauma surgeons and therefore there was no learning curve for the surgeons.

Almost all the complications (27 out of 28) were medical complications. Patients with hip fractures are very frail elderly people with multiple comorbidities. This is the reason why they are slow to recover and why they are vulnerable to medical complications. Ten percent of the patients with hip fractures will die in the first 30 days and a third of them will die within the first year (3). All 6 deaths in this study were due to medical complications or advanced age and frailty (see section 8.2). Similarly, all SAEs were medical complications associated to prolonged bed rest and frailty.

8.4 Final telephone call review

According to the protocol, all patients should receive a telephone review 6 months after the last (12 week) follow-up review. The purpose of this review was to identify any possible adverse events since the last review. The telephone review was delayed for all patients, as it was not included in the CRF and it was not carried out at the end of the follow-up. This protocol deviation was reported to the research ethics committee, and it was advised that it could take place at a later stage.

The telephone review was carried out on average 21.4 months from surgery (range 13.6 – 28.5 months).

At the time of the telephone review, 29/60 patients (48.3%) were still alive:

- 14 patients in the nail group and 15 patients in the DHS group.
- 24 patients with AMTS \geq 8 and 5 patients with AMTS $<$ 8.

Out of the 29 patients alive:

- 17 patients (58.6%) completed the telephone review.
- In 5 patients (17.2%) the telephone review was completed by their carers.
- 2 patients (6.9%) declined having a telephone review.
- 5 patients (17.2%) did not answer the phone on multiple times.

Out of the 22 patients who completed the telephone review (10 in the nail group and 12 in the DHS group, 17 with AMTS \geq 8 and 5 with AMTS $<$ 8), no new adverse events were reported.

At the time of the telephone review:

- 17 patients (77.3%) lived in their own house, 2 (9.1%) lived with family, 2 (9.1%) in a residential home and 1 (4.5%) in a nursing home.
- 1 patient (4.5%) mobilized without aids, 9 (40.9%) mobilized with one stick, 10 (45.5%) mobilized with a frame and 1 (4.5%) was bedbound (1 patient was very deaf and could not answer the questions).
- 13 patients (59.1%) had no residual hip pain, 5 (22.7%) had some ongoing pain and 3 (13.6%) had moderate to severe pain (patient required GP review) and 1 patient could not answer the questions.
- None of the patients had further hospital admissions.

Since we checked whether the patients were alive or not for the telephone review, we were able to calculate mortality rates up to 1 year (Table 32). We excluded the patients who were withdrawn during the study (i.e. 4 patients).

Overall, 14/56 patients (25%) had died within one year from their operation. 1-year mortality was 8/28 (28.6%) for the nail group and 6/28 (21.4%) for the DHS group ($p=0.759$).

Split by AMTS, 1-year mortality was 4/36 (11.1%) in patients with AMTS \geq 8 and 10/20 (50%) in patients with AMTS $<$ 8 ($p=0.037$).

Table 33: Mortality rates

| Mortality, n/N (%) | Nail | DHS | p-value |
|--------------------|--------------|--------------|---------|
| In-hospital | 3/28 (10.7%) | 1/28 (3.6%) | 0.611 |
| 3 months | 4/28 (14.3%) | 2/28 (7.1%) | 0.669 |
| 1-year | 8/28 (28.6%) | 6/28 (21.4%) | 0.759 |

8.5 Safety conclusions

- It was safe to conduct a randomised trial including patients with and without cognitive impairment.
- Highlighting in protocol all required trial safety evaluations will reduce the risk of these procedures being missed in future.
- This trial confirmed that patients with hip fractures are at high risk for developing medical complications or not surviving.
- There were very limited number of surgical related complications; this was probably because both implants used are well established treatments for hip fractures. Moreover, all surgeons were senior, and all patients were treated by a multidisciplinary specialist team.

Chapter 9

Discussion

Current evidence on the management of intertrochanteric fractures is based mainly on trials with patients with intact cognition (17). However, a third of patients with hip fractures has a degree of cognitive impairment. Moreover, there is a lack of feasibility studies in the literature on hip fractures and as a result, the majority of the functional outcome measures used in trials with hip fractures have used outcome measures which are not appropriate for this population (26). Therefore, this current feasibility study aimed to include patients with cognitive impairment and to report on the outcomes specifically for this subgroup population.

Although it was possible to recruit the target number of participants, it was not possible to retain 90% of the patients in the study by week 4 follow-up visit. The main reason for the high dropout numbers was high mortality in the group with AMTS<8 (4 deaths, 6.7%) and withdrawal of patients who received a long nail (3 patients, 5%) due to extension of the fracture line in the subtrochanteric area, which was not evident pre-operatively. Secondly, the TUG test was not a suitable tool to assess mobility at 4 weeks post-operatively since not all the patients were able to perform it at this time point. Eight (16%) out of the 50 patients who attended week 4 follow-up visit were not able to walk 6m safely. Secondary objectives included surgery related variables, admission related variables, functional mobility, and radiographic outcomes. Although the primary objective was not to identify differences between the two groups, there was preliminary proof-of-concept that pain levels were lower in the nail group at 2 weeks as well as preliminary proof-of-concept that radiographic outcomes (neck collapse, medialisation and shortening) were better in the nail group at all time points. Readiness to discharge appeared also to be shorter in the nail group (especially in the AMTS<8 subgroup), however, this finding was not translated to a shorter hospital stay. Moreover, readiness to discharge is a difficult variable to define clearly since it depends on the judgement of the physiotherapy team. Otherwise, there were no differences between the patients treated with a nail or a DHS with regard to the surgery related or functional outcomes.

9.1 Current RCTs on intertrochanteric fractures and patients with cognitive impairment

Although there is an abundance of studies on hip fractures, very few studies have included or have reported outcomes on patients with cognitive impairment. A recent systematic review has shown that only 26% of the studies on hip fractures included patients with cognitive impairment and only 2 studies reported outcomes for this population (17). It is now well understood that 1 in 3 patients with a hip fracture has a degree of cognitive impairment. Omitting this population from clinical trials or ignoring them when reporting outcomes reduces the external validity of the trials.

A recent meta-analysis exclusively on type A2 fractures, included 6 RCTS comparing intramedullary vs extramedullary fixation (19). Out of the 6 trials, only one (16.7%) included clearly patients with cognitive impairment (Table 34). Two trials screened patients for dementia but it is not clear if they included them or not; in the study of Reindl et al., patients with severe dementia were excluded but severe dementia has not been defined and in the study of Verettas et al., it is not clear whether patients with dementia were included, although all patients had a MMSE and the average score was 22-23 (as a reference, severe dementia is MMSE<10 and moderate dementia is MMSE 10-20). Moreover, none of the studies reported outcomes specifically for patients with cognitive impairment. Therefore, it can be said that the current evidence on the management of intertrochanteric AO/OTA type A2 fractures either ignores patients with cognitive impairment or there is no clear evidence whether patients with cognitive impairment have the same outcomes with patients with normal cognition.

Similar observations come from bigger meta-analysis on all types of intertrochanteric fractures. The most recent and largest meta-analysis comparing intramedullary vs extramedullary fixation included 43 RCTS and enrolled 6911 patients (18). Only 10 of the RCTS (23.3%) included patients with dementia. Therefore, we can conclude that the majority of RCTS on intertrochanteric fractures exclude or ignore a big sub-population of patients with these fractures.

Several screening tests have been used in RCTS to assess participants' cognitive status. The most commonly tests used include the Mini-Mental State Examination (54,116), the clock drawing test (112) and the Abbreviated Mental Test Score (113). The MMSE is considered the gold standard screening tool. It consists of 30 questions, it takes 5-10m to administer and scores range from 0-30. Its use has decreased recently due to copyright issues (15). In this study we used the AMTS which is quick and easy to do, and it is also routinely performed in all patients with a hip fracture in the UK. Moreover, the AMTS is the same effective as the MMSE (140).

Although the AMTS is a good tool to screen for cognitive impairment, it does not allow to grade the level of cognitive impairment. On the other hand, the MMSE allows staging of dementia according to the score achieved; scores of 30 suggest no dementia, scores 26-29 suggest questionable dementia, scores 11-20 suggest moderate dementia and scores 0-10 suggest severe dementia (141). In this study there were patients who were unable to communicate and answer simple questions or were unable to follow simple instructions and perform the TUG test. In a future trial, the level of severity of cognitive impairment should be considered and those patients with severe dementia should probably be excluded from secondary outcome measures which are too difficult for them to perform. On the contrary, the primary outcome measure should be available for all the patients and therefore it should be completed even by patients with severe dementia. Outcome measures which have a proxy version would be ideal for this purpose.

In this study, different outcome measures, depending on the cognitive status, were used to assess functional mobility and quality of life. The LEM was used for patients with normal cognition and the DEMQOL for patients with cognitive impairment. The LEM is a patient-reported outcome measure and thus it would be too difficult or impossible to use in patients with cognitive impairment. For this reason, the DEMQOL was used for patients with $AMTS < 8$. DEMQOL has been shown to be a reliable tool of health related quality of life in patients with dementia (32); however it is yet to be validated in patients with hip fractures. Other studies have used several other outcome measures, such as the FIM, LEM, EQ-5D, VAS (Table 34). However, only the EQ-5D has already been validated in patients with cognitive impairment (30). Further research is required in the development of suitable outcome measures for use in patients with hip fractures with cognitive impairment.

Table 34: Characteristics of other RCTs on intertrochanteric A2 type fractures.

| | Type of fracture | Treatments compared | Included dementia | Trial retention rates | Clear primary outcome | Secondary outcomes |
|----------------------|------------------|------------------------------|------------------------|--|-----------------------|--|
| 2015 Reindl | A2 | DHS vs (InterTAN/TFN/ Gamma) | Not clear ¹ | 6w: 194/204 (95.1%) 3m: 181/204 (88.8%) 12m: 167/204 (81.9%) | LEM | FIM, TUG, 2MWT, Radio |
| 2015 Zehir | A2 | PFNA vs DHS | No | 6m: 141/198 (71.2%) | Not clear | Surgery details, Radio, functional status |
| 2014 Aktselis | A2 | Gamma vs AMBI SHS | No | 12m: 71/80 (88.8%) | Not clear | Union, Parker score, Barthel index, EQ-5D |
| 2010 Verettas | A2 | (Gamma or Endovis) vs DHS | Not clear | No | Not clear | Surgery details, LOS, VAS, complications |
| 2010 Xu | A2 | PFNA vs DHS | Unknown | 3m: 98/106 (92.5%) 12m: 83/106 (78.3%) | Not clear | Surgery details, LOS, complications, mobility score, Radio |
| 2010 Barton | A2 | SHS vs Gamma | Yes | 12m: 151/210 (71.9%) | Implant failure | EQ-5D, re-operations, TAD, LOS |

¹patients with severe dementia were excluded – severe dementia was not defined

9.2 Is the TUG test a suitable measure outcome to be used in RCTs on hip fractures?

This study hypothesized that the TUG test would be a good physical assessment tool to reveal preliminary evidence of treatment effect between the groups. However, the results of the study have revealed the following issues: 1. The test proved to be too difficult for patients to perform and there were patients unable to perform it at 4 weeks or even at 12 weeks (performance rate 42/50 and 39/44 respectively), 2. There was large variability in the TUG times and comparison between the groups was difficult (range from 13sec to 381sec).

The TUG test is a well-established physical assessment measure of functional mobility and it has already been used in similar RCTs on intertrochanteric hip fractures (22,23,112). Similar to this study, other studies have reported similar or even lower rates of patients failing to perform the test. In particular, Sanders et al. reported that only 56.4% of the patients were able to perform the TUG test at 4-6 weeks from surgery and this rate increased to 74.2% at 3 months and to 83.9% at one year (22).

The patients of this study needed more time on average to perform the test than in other studies. The average time of TUG test in the combined arm group was higher than the times reported in other studies at similar time points (Table 35). This was probably because in this study there was no upper limit for the TUG test. However, other studies considered the test successful only if times were < 210sec (112). Also

other studies included only cognitive intact patients and this may have led to shorter times (22). Finally, because our study had a significantly higher proportion of patients able to perform the test, it could be that there was a lower threshold to abandon the test in other studies than in this study. All the above reasons may explain the longer TUG times observed in this study.

The TUG test has already been studied extensively in patients with hip fractures. Although there are no reported expected or normal times, the TUG test has been recommended as a predictor for falls and also for assistance with mobility in the elderly (38). There is published evidence to suggest that TUG times are longer with increasing age and with cognitive decline (142,143). A big Canadian study in elderly people has found that patients with cognitive impairment were more likely not to be able to perform the test at all than cognitive intact patients (46). Moreover, this study concluded that the TUG test is infeasible when administered in a heterogeneous elderly population and its reliability is not acceptable for routine use.

Another RCT on intertrochanteric fractures, reported that only 38% of the patients were able to perform the TUG test at day 5 postoperatively; particularly, 25% of the patients were not able to rise at all from the chair. At 12 months, only 314/373 (84.2%) of the patients were able to perform the test. They concluded that the TUG test is not a suitable tool to assess functional mobility in patients with hip fractures either in the early postoperative period or even at 12 months (42).

In conclusion, the findings of this study agree with the data already published in the literature and suggest that the TUG test is not a suitable test to assess functional mobility in patients with hip fractures at the immediate postoperative period or later down the line at 3 months. It is a difficult test to perform and it has large variability which makes it difficult to detect a difference between the groups. Assessing this test at later time points continues to be difficult for patients; besides, this is not ideal in a study including people with hip fractures who have high mortality and attrition rates are expected to be high.

Table 35: Results of Timed Up and Go test in other randomised control trials.

| | Able to perform at 4-6 weeks (%) | Able to perform at 3 months (%) | Able to perform at 12 months (%) | TUG time in sec at 4-6 weeks (range) | TUG time in sec at 3 months (range) | TUG time in sec at 12 months (range) |
|-----------------------|----------------------------------|---------------------------------|----------------------------------|--------------------------------------|-------------------------------------|--------------------------------------|
| Sanders et al. | 127/225 (56.4%) | 161/217 (74.2%) | 162/193 (83.9%) | 27.5 (9-217) | 21 (4-165) | 18 (4-260) |
| Reindl et al. | Not reported | Not reported | Not reported | 34-48 | 26 | 19-20 |
| Matre et al.* | 258/601 (42.9%)** | Not reported | Not reported | Not reported | 29 | 25-27 |
| PET | 42/50 (84%) | 39/44 (88.6%) | NA | 56 (13-381) | 36 (14-229) | NA |

PET: Pterochantheric Endovis trial, *Times over 210sec were considered not successful, ** Performed at day 5 postoperatively

9.3 Retention rates in clinical trials on hip fractures

In this study, it was not possible to retain 90% of the patients in the trial by week 4. The retention rate for this study was 50/60 (83.3%) at 4 weeks and 49/60 (81.7%) at week 12. Split by AMTS, the retention rate was 34/38 (89.5%) for patients with AMTS \geq 8 and 16/22 (72.7%) for patients with AMTS $<$ 8 at week 4. At week 12, retention rates changed slightly for patients with AMTS \geq 8 (35/38, 92.1%) and decreased further for patients with AMTS $<$ 8 (14/22, 63.6%).

We concluded that, although it was not feasible to achieve an overall 90% retention, this would have been possible if we had included only patients with AMTS \geq 8.

The main reasons for high drop-out rates in patients with AMTS $<$ 8 were deaths and withdrawals. It is difficult to avoid deaths in this patient population due to the high mortality and comorbidity. However, dropouts due to ineligible fracture patterns can be avoided by randomising patients in theatres, after the patients are screened on the traction table.

Most studies have reported retention rates at 12 months (Table 36). Only 2 studies reported retention rates at earlier stages; Reindl et al. reported retention rates at 6 weeks and at 3 months, and Xu et al. reported retention rates at 3 months. Both studies had better retention rates than this study; Reindl et al. reported retention rates of 95.1% at 6 weeks and 88.8% at 3 months (23) whereas Xu et al. reported a retention rate of 92.5% at 3 months (111). However, both studies have not included patients with dementia (in the study by Reindl et al. 'patients with severe dementia were excluded'; there was no mention of patients with dementia in the paper from Xu et al.). In our study, all deaths occurred in the AMTS $<$ 8 patients. Dementia is a known risk factor for high mortality in hip fractures; therefore, by

excluding this subpopulation, retention rates are expected to be higher. Also, it seems that the patients recruited by Xu et al., had fewer comorbidities than the patients of this study; the proportion of patients with ASA 3/4 was only 30%, whereas the proportion of patients with ASA 3/4 in the current study was 70%. This difference could have affected retention rates as well.

It is important for the researchers to be aware of retention rates and particularly the high drop-out rates in patients with AMTS<8. If dropouts are expected to be around 30% as in this trial, then choosing suitable efficacy measures and assessing outcomes at suitable time points will lead to low rates of missing data and thus better quality of data for analysis. Identifying surrogate variables that can be assessed at early stages will result in more complete data than variables which are assessed at later stages. Also, being aware of the expected dropouts will help in power analysis of the sample size.

9.4 Primary outcomes in RCTs on intertrochanteric fractures

9.4.1 Primary outcomes in RCTs on A2 hip fractures

This study hypothesized that the TUG test can be a potential primary outcome measure; our data showed that the TUG test is not a suitable efficacy measure for a trial on hip fractures. Other studies have used other primary outcomes such as functional mobility outcome scores, such as the LEM (22,23), the Functional Independence Measure (FIM) (23), or pain scores such as the Visual Analogue Score (VAS) (112,116) or complications (54,110) (such as implant failure) (Tables 36 and 37). Other secondary efficacy measure assessments used in RCTs include intraoperative details, blood loss and blood transfusion requirements, length of stay, the Harris Hip Score (HHS), 2-minute walk test, Parker mobility score, the Barthel index, the EQ-5D, reoperation rates or other radiographic variables.

The main issues with intramedullary nailing and other internal fixations used to be peri-prosthetic fractures or metalwork failure (such as cut-out). As a result, the focus on early RCTs was on metalwork complications and reoperations. However, newer implant designs have led to a significant decrease in the number of periprosthetic fractures and cut-outs (72,144). As a result, more recent RCTs have used functional mobility scores as well as radiographic outcomes when comparing the effectiveness of different implants. Radiographic variables have the advantage that they can be assessed irrespectively of the patient's cognitive status. However, there is evidence to suggest that radiographic outcomes do not always correlate with better functional mobility (22,23). Moreover, measurements are affected of the degree of magnification, which depends in a number of factors which cannot always been controlled in daily clinical practice (i.e. the positioning of the x-ray tube in relation to the part of the limb imaged).

Therefore, although radiographic variables are important in assessing treatment effect between two implants, they are not ideal primary outcome measures.

A physical performance test (such as the TUG test, the 2-minute walk test or the 30sec sit to stand test) is considered a more objective tool in assessing functional mobility than a self-reported measure (145). As it is shown in Table 37, both the TUG test and the 2-minute walk test have already been used in RCTs in hip fracture trials (22,23,112). The main problem with the TUG test in this trial was that it was too difficult for some patients to perform even at 12 weeks and the results varied significantly among patients. Moreover, times continued to improve till week 12 and therefore the medians of the groups at that point did not normalise.

The 2-minute walk test and the 30sec sit to stand test are less physical and so they should be easier for patients to perform. Both these tests have been validated in patients following knee arthroplasty but not in patients with hip fractures (146,147). In these studies, both tests have been used to assess walking ability, lower extremity function and strength following joint replacement surgery and their reliability has been shown to be excellent. Another advantage of these tests is that even if patients are unable to perform, they will still get a value (which will be zero meters or zero sit-to-stand repetitions) instead of having no values as in TUG test. Therefore, further research is required so that these physical performance tests are validated in patients with hip fractures before they are used in clinical trials.

Patient-reported outcome measures are standardised and validated questionnaires that are completed by the patients with the aim to measure their perceptions on their functional status and wellbeing. Not only patients are directly involved in this evaluation but also activities or functions performed in their daily life, and not in the clinic, are assessed. For this reason, patient-reported outcomes are considered person-centred outcomes (148).

Several patient-reported outcomes have already been used in RCTs on hip fractures such as the LEM, the FIM, the EQ-5D, the HHS and the Barthel index (Table 37). In this study we used different questionnaires depending on the AMTS of the patients; patients with $AMTS \geq 8$ used the LEM and the LHS and patients with $AMTS < 8$ used the DEMQOL. We were able to collect good quality data (high completeness rates) for the LEM and the LHS (total completion rates of 92%). However, data completion rates were significantly lower for the DEMQOL and DEMQOL-carer (62% and 71.1% respectively). The main reasons for missing data in DEMQOL questionnaires were due to deaths and withdrawals. The 9% difference between the QEMQOL and DEMQOL-carer was due to poor communication skills in patients with advanced dementia.

This difference, though, shows that a questionnaire that can be answered by a caregiver will result in higher data completion rates than a questionnaire that can be answered only by the patient.

With regard to the LHS questionnaire, not only it hasn't yet been validated in patients with hip fractures, but also the domains of occupation, social integration and economic self-sufficiency didn't apply to the studied population. Moreover, the values observed in this study did not change during the study period (mean baseline score was 0.7, decreased to 0.6 at 2-4 weeks and increased to 0.7 by 12 weeks). For all these reasons, the London Handicap Score is not supported for use in a study on hip fractures by the current trial.

Intraoperative outcomes (such as operation time, blood loss, blood transfusion requirements) are important factors to be compared between two treatments however they have not been used as primary outcomes in RCTs so far. This is possibly because these outcomes do not correlate with shorter overall stay or better function. Another difficulty of using these variables as primary outcomes is that it is difficult to define a level of meaningful clinically significant difference; for example, it is possible to show that a 50ml difference in blood loss is statistically significant, but it is not possible to know whether this difference is clinically significant, unless this correlates with shorter hospital stay or another functional outcome or another key variable.

9.4.2 The optimal primary outcome measure

The optimal primary outcome measure in an RCT on intertrochanteric fractures, as in every RCT, should be the most important variable in the study. More than that, it should be available in all subjects at the desired time point, it should be dependent on the clinical effect of the investigated interventions, and it should have acceptable measurement properties.

When planning a study in patients with hip fractures, the following issues should be considered: 1. High attrition rate due to high mortality, 2. High incidence of cognitive impairment, 3. Very frail patients with limited abilities to complete physical performance tests, and 4. Slow and lengthy recovery period.

The length of hospital stay or readiness for discharge (if correlated with a shorter length of stay) are, potentially, variables that can be assessed early, and they are important. In this study there was preliminary proof-of-concept difference between the groups for readiness of discharge for patients with AMTS<8. Further unplanned analysis showed that there was preliminary proof-of-concept difference between the groups for all patients with lower levels of confidence (80% confidence intervals). However, the main difficulty in using the readiness for discharge as an outcome in a future study is the difficulty to

define clear criteria for when a patient is ready for discharge. For example, a patient who normally lives in a nursing home is ready for discharge as soon as there are no acute medical problems that require hospital stay. On the contrary, a patient who lives alone in a house with stairs is ready for discharge when they will be able to climb the stairs safely. Consequently, readiness for discharge can mean different level of independence for different patients.

Regarding the optimal patient-reported outcome measure, ideally the same tool should be used for all patients (with and without cognitive impairment). The LEM has been validated in patients with hip fractures and it assesses functional mobility but there is no proxy version and therefore it will not be possible to be completed by patients with cognitive impairment. Therefore, it is recommended only for patients with intact cognition. Therefore, none of the outcome measures used in this study can be recommended for use in a future study and other PROMS need to be considered.

A good patient reported outcome measure for use in a future study should be measurable in both patients with and without dementia. Such an outcome could be the EQ-5D. It has a version that can be answered by a proxy on behalf of the patient, so it would be suitable for those with AMTS<8. It has already been validated in patients with cognitive impairment and it has been shown to perform well in evaluating health related quality of life in both patients with and without dementia (149). Moreover, for those who died during follow-up, an EQ-5D index value of zero could be recorded. Finally, it has a telephone interview version which can be administered through the phone. Therefore, outcome measures such as the EQ-5D should be considered for use in a future study.

Regarding physical performance tests, the 2-minute walk test or the 30sec sit-to-stand test could be used alternatively to the TUG test. Both tests are physically easier than the TUG test and they have an upper limit when the test is stopped. Also, an index value of zero could be used for those patients who are bedbound and cannot complete the test. However, both these measures are yet to be validated in patients with hip fractures.

Overall, considering the results of this study, it is not possible to make a recommendation about the optimal primary measure. Alternative measures that can be assessed and validated in a future study include the EQ-5D, the 2-minute walk test and the sit-to-stand test.

9.5 Secondary outcomes

All comparisons were made with the results reported in 6 other RCTs which included exclusively patients with A2 type fractures (19). If a variable was not reported on these 6 RCTs, then comparisons were made with RCTs not exclusively on A2 type fractures.

9.5.1. Surgery related outcomes

Operative time

The average operative time was 46.2min in the nail group and 48.9min in the DHS group and there was no significant difference between the groups. Operative times in other studies have varied between 42-68.5min in the nail group and between 45-75.5 in the DHS group (108,109,111,116). Two studies found that operative time was statistically significantly shorter in the nail group (108,109) and one study found that operative time was statistically significantly shorter in the DHS group (111). A fourth study found that operative times were comparable between the groups (116). Overall, the operative times recorded in this study were in accordance with the operative times recorded in other studies.

Blood loss

To record blood loss accurately, we measured the amount of blood in the suction tube and also the amount of blood in the surgical swabs (weight of swabs).

We found comparable blood loss in suction between the groups (nail 83.2ml, DHS: 126.7ml) and comparable blood loss in surgical swabs between the groups (nail: 76.6g, DHS: 79.1g). Three other RCTs have reported blood loss (108,111,116). The blood loss reported in these studies varied between 140-220 ml in the nail group and between 200-472ml in the DHS group. Two studies found that the blood loss was significantly higher in the DHS group than in the nail group (108,111) and in the third study blood loss was comparable (116). This was confirmed by a meta-analysis by Zhu (19).

A future study should aim to capture intraoperative blood loss in detail, calculating the total blood loss through suction and swabs.

Blood transfusion requirements

Similar proportions of patients in both groups (44.8% in the nail group and 53.6% in the DHS group) required blood transfusion. It is worth noting that five patients in the nail group and one patient in the DHS group had baseline haemoglobin less than 100g/L and this potentially predisposed more patients to

blood transfusion in the nail group. A future full-scale trial with a larger sample will decrease the chances of unequal groups in baseline.

Similarly, high proportions of patients requiring blood transfusion have been reported in other RCTs (54,111). In the study by Xu et al., 87.3% of the patients treated with a DHS required blood transfusion whereas only 37.2% of the patients treated with a nail required blood transfusion. This difference was statistically significant. In the study by Barton et al., both groups had comparable requirements in blood transfusion (nail 51%, DHS 42%).

9.5.2. Hospital length of stay and readiness for discharge

The average hospital stay in this study was comparable in the two groups (21 days in the nail group and 22 days in the DHS group).

Length of stay has been reported in 5 other RCTs and it varied between 7 and 32 days in the nail group and between 7.4 and 31 days in the DHS group (54,108,109,111,116). Only in one RCT the length of stay was found to be statistically significant higher in the DHS group (nail 7.2 days, DHS: 8.6 days) (108); however, it is arguable whether this is a clinically significant difference.

Readiness for discharge has not been reported in other RCTs. With readiness for discharge, we wanted to assess duration of stay only due to medical reasons. Usually, social reasons prolong the length of stay and they can mask any difference between the groups. We found that there was statistically significant difference in readiness for discharge in patients with AMTS<8. However, further work is required in determining clear and easily measurable criteria about when a patient is deemed ready for discharge.

9.5.3. Pain level assessment

Pain levels were assessed using the Numeric Rating Scale. There was statistically significant difference in favour of the nail group at 2 weeks from surgery. At 4 weeks and 12 weeks, pain levels were comparable in the two groups. However, unplanned analysis showed that, there was preliminary difference in favour of the DHS group at 12 weeks with lower levels of confidence (Table 28).

One other RCT has used the Visual analogue scale and found similar levels of pain between the groups between day 1-5 and between day 6-10 (116).

Other RCTs that have included all types of intertrochanteric fractures (types A1, A2 and A3) have assessed pain levels using the VAS (112) and the Charnley pain score (110). Both these studies reported no significant differences between the groups at 3 months and 12 months.

Because it is difficult to ask a patient with cognitive impairment to rate the level of pain on a scale 1 to 10, we also recorded all analgesia requirements within the first two weeks. This was reported as morphine equivalent dose.

There was descriptive difference in analgesia requirements in favour of the nail group. However, further unplanned analysis showed that there is potential proof-of concept difference in favour of the nail group at lower levels of confidence, particularly for patients with AMTS<8.

Analgesia requirements have not been reported in other RCTs.

9.5.4. Timed Up and Go test

We found that there was no difference in the TUG times between the groups at all time points.

The TUG test has been used in one other RCT (23). Similar to our study, TUG times were comparable between the groups at 3 months and 12 months (Table 36).

The TUG test has been used in other RCTs that have included all types of intertrochanteric fractures (22,112). Both these studies reported comparable times between the groups at 3 and 12 months (Table 36).

9.5.5. Patient-reported outcome measures

LEM

In this study, lower limb motor function was assessed with the LEM questionnaire in patients with ATMS \geq 8. The higher the score, the better the function. Patients treated with a nail had descriptively higher scores at 2 weeks (41.7 vs 31.3), 4 weeks (48.2 vs 43.1) and 12 weeks (61.3 vs 54.2); however, none of these differences were statistically significant.

One other RCT has also used the LEM (23). Like this study, the nail and the DHS group had comparable LEM scores at 3 months (nail 56 vs DHS 55.4) and at 12 months (nail 66 vs DHS 64.4).

Similarly, the study from Sanders et al. which included A1 and A2 types of intertrochanteric fractures showed no difference in the LEM score between the groups at 3 months (nail 58.3 vs DHS 58.2) and at 12 months (nail 63.1 vs DHS 63.4) (22).

DEMQOL

Quality of life was assessed with DEMQOL questionnaire in patients with AMTS<8. DEMQOL consists of 2 questionnaires: one is completed by the patient and one by the caregiver (proxy). It mainly assesses

emotion, memory, ability to carry out activity of daily living and perception of quality of life. It has been shown to be an accurate measure of individual differences in health related quality of life in patients with dementia (32). However, it has not yet been validated in patients with hip fractures. Higher DEMQOL scores indicate higher perceived quality of life.

In this study, patients treated with a nail had descriptively higher DEMQOL and DEMQOL-carer score than patients treated with a DHS at 2 and 12 weeks. At 4 weeks, DEMQOL score was higher in the DHS group than in the nail group; however, DEMQOL-carer score continued to be higher in the nail group than in the DHS group.

DEMQOL hasn't been used in other RCTs before. Moreover, no other RCT on intertrochanteric fractures has used a specific questionnaire for patients with cognitive impairment. Further work is required in order to assess its validity and reliability in patients with hip fractures.

9.5.6. Other functional outcome scores used in other RCTS

Parker mobility score

Three RCTs used the Parker mobility score (18,86,94). Mobility scores range between 0-9 and the higher the score, the more mobile (independent) the patient is.

Two studies compared the mobility score in each group (109,111) whereas the third study compared the change in the mobility score (54). Only in the study by Xu et al. there was statistically significant difference in the mobility score in favour of the nail group (nail 5.6 vs DHS 4.4). Mobility scores and change in the mobility score were comparable in the other two studies.

EQ-5D

Two studies used the EQ-5D to assess general quality of life (54,109).

Barton et al. reported comparable EQ-5D at 12 months between the groups (nail 0.37 vs DHS 0.46) whereas Aktseis et al. found significant improvement in the EQ-5D only at 12 months in favour of the nail group (nail 0.90 vs DHS 0.78); there was no statistical difference between the groups at 4 weeks and 3 months.

Barthel index

The Barthel index is a scale that measures performance in daily activities. It assesses degree of dependence in 10 areas; each area is given a grade from 0 to 10, (0 = unable to perform, 10 = able to

perform independently). The 10 areas include feeding, bathing, grooming, dressing, bowels, bladder, toilet use, transfers, mobility, and stairs. The questionnaire is completed by the investigator.

Barthel index was used by one other RCT (109). This study found that there was difference in the Barthel index between the groups at 12 months (nail 89.7 vs DHS 81.1) but not at 4 weeks or 3 months. It is worth noting, that in this study, these results correlated with the EQ-5D.

FIM

The Functional Independence Measure (FIM) is a tool used to assess patient's disability, and change in response to rehabilitation. It is an 18-item questionnaire that aims to assess and grade the degree of functional independence in activities of daily living. Each item is scored 1-7; 1 indicates total assistance, 7 indicates complete independence. Higher scores indicate higher independence with activities of daily living.

The FIM was used by one other RCT (23). This study reported comparable FIM scores between the groups at 3 months (nail 99 vs DHS 106) and at 12 months (nail 106 vs DHS 111).

2m walk test (2MWT)

The 2MWT is an assessment of walking capacity and functional mobility. It is a short version of the 6min walk test or the 12min walk test. The patient is asked to walk as fast as possible for 2min and the distance is recorded.

One other RCT has used the 2MWT (23). There was no statistically significant difference between the groups at 3 months (nail 62m vs DHS 71m) and at 12 months (nail 80m vs DHS 81m).

The 2MWT was also used in the study by Sanders et al. (22) (which included A1 and A2 types of intertrochanteric fractures). Likewise, there was no difference between the groups at 6 weeks, 3 months, 6 months and 1 year (nail vs DHS: 51 vs 43.5, at 6 weeks, 56 vs 61 at 3 months, 62 vs 66 at 6 months, 64 vs 70 at 1 year). Interestingly, although the 2MWT seems to be an easier to perform test than the TUG test, similar proportions of patients were able to perform the two tests at each time point (at 6 weeks: 2MWT: 51-55% vs TUG: 55-58%, at 3 months: 2MWT: 71-76% vs TUG: 71-77%, at 6 months: 2MWT: 78-82% vs TUG test: 79-92, at 12 months: 2MWT: 73-85% vs TUG: 74-88%).

9.5.7 Mortality

In this trial, in-hospital mortality was 7.1% (10.7% in the nail group and 3.6% in the DHS group) (Table 33). At 3 months, overall mortality increased to 10.7% (14.3% in the nail group and 7.1% in the DHS group). At 1 year, mortality increased further to 25% (28.6% in the nail group and 21.4% in the DHS group).

Similar rates of mortality have been reported in other RCTs; Barton et al. reported in-hospital mortality of 21% in the nail group and 10% in the DHS group, whereas Verettas et al. reported in-hospital mortality of 1.7% for both groups.

Most of the other RCTs have reported mortality rates at 12 months which ranged from 3.9-32% (23,54,108,109,111). It's important for the researcher to be aware of the mortality rates for the designing of a future study as this can affect attrition rates. Moreover, it's useful to be aware of the mortality rates when choosing a primary outcome measure and when it will be assessed.

9.5.8 Radiographic results

TAD

The average TAD was significantly higher in the nail group than in the DHS group (18.2mm vs 14.9mm, $p=0.044$). Moreover, four patients in the nail group had $TAD>25\text{mm}$ whereas none of the patients with a DHS.

Other RCTs have reported comparable TAD between nail and DHS groups (23,54,108).

The TAD was originally described for extramedullary devices (122). Although the evidence is limited, comparative retrospective studies have shown that the TAD can be considered a significant predictor of metalwork failure also for intramedullary devices (98,150–152). Moreover, a $TAD>25\text{mm}$ has also been found to be predictive risk factor for metalwork failure for intramedullary nails.

Although the patients in the nail group had statistically significant higher TAD than the patients in the DHS group, the mean TAD was 18.2mm which is lower than the 25mm which is the cut-off for metalwork failure. A possible reason for the higher TAD in the nail group, is due to the dual femoral screw design of the Endovis nail. In order to insert two cephalic screws in the femoral head, the inferior screw was inserted slightly more inferiorly than a single cephalic screw. Since the inferior screw was used for the calculation of the TAD in this study, it can be argued that a higher TAD would be expected.

Neck-shaft angle

The neck-shaft angle was measured at 2, 4 and 12 weeks. The average neck-shaft angle was persistently higher in the DHS group (at 12 weeks: nail 126.8° vs DHS 133.6°). There was no significant change in the neck-shaft angle within each group with time.

Similar to this study, Matre et al. found that the neck-shaft angle was more varus in the nail group than in the DHS group (131° vs 138°) (112). Likewise, Pajarinen et al. also found that the neck-shaft angle was persistently more varus in the nail group than in the DHS group at 6 weeks and 4 months (6 weeks: 121° vs 129°, 4 months: 121° vs 130°) (153).

Femoral neck shortening

Femoral neck shortening was assessed using two different measuring techniques:

1. Cephalic screw collapse.
2. Neck collapse.

The main difference between the 2 measuring techniques is that the first technique compares the length of the neck in two different time points whereas the second technique compares the length of the neck between injured and uninjured hips. In this study, the first post-operative radiograph was taken at 2 weeks. By this point, patients were expected to have started to mobilise. Consequently, any neck collapse by this time point was not observed, since no radiograph had been taken. To avoid this in future, we suggest post-operative radiographs to be taken the first day after surgery, if this variable is to be used. Since this technique of measuring neck collapse was not accurate, the rest of the discussion for neck collapse will be based on the measurements by comparing shortening of the femoral neck to the contralateral side.

Neck collapse was found to be significantly different in the 2 groups at all time points; the neck collapse increased from 1.2mm in the nail group and from 9.5mm in the DHS group at 2 weeks to 2.9mm in the nail group and 12.3mm in the DHS group at 12 weeks.

Neck collapse has also been reported in the study by Reindl et al. (23). However, in their study X-rays were taken immediately postoperatively. They reported that the average neck length shortening was 10mm in the DHS group and 2mm in the nail group. These results are similar to the findings in our study, but when using a different measuring technique.

Medialisation

In this study, we found that the DHS group had higher degree of medialisation at all time points. Moreover, more patients in the DHS group had medialisation >5mm at all time points.

Matre et al. have also reported that more patients in the DHS group had >5mm medialisation at 12 months than patients in the nail group (112).

Leg shortening

We calculated the leg shortening in the AP pelvis X-ray taking into account the distance between the transischial line and the most medial point of the lesser trochanter, as this has been described in the literature (132).

We found that leg length was significantly higher in the DHS group than in the nail group (average leg shortening nail 5.7mm vs DHS 11.4mm).

These results agree with similar results from other studies. Zehir et al. reported that statistically significantly more patients in the DHS group had 5-10mm femoral shortening (nail 14% vs DHS 56%) than patients in the nail group (108). Similarly, Xu et al. reported that the average shortening of the femur was 2.6mm in the nail group and 4.8mm in the DHS group, which was a statistically significant difference (111).

Fracture healing

We assessed fracture healing using the RUSH score.

By 3 months, the average RUSH score seemed to be descriptively higher in the DHS group than in the nail group (nail 22.9 vs 24.5). Moreover, more patients in the nail group had RUSH score <18 (suggestive for non-union) than in the DHS group (nail 76.2% vs 91.7%).

We have to be careful when interpreting these preliminary results as it is early to assess bone healing of hip fractures at 3 months.

No other RCT on type A2 intertrochanteric fractures has used the RUSH score so far. Only one other RCT has reported results on fracture healing; it was reported that all fractures united by 12 months (109). The RUSH score was used in this study in an attempt to report bone healing in a more systematic and standardised way.

9.5.9 Orthopaedic-related complications

In this study there was one orthopaedics-related complication; one patient sustained an atraumatic undisplaced fracture at the level of the distal cephalic screw (see section 8.2).

During the trial period, there were no screw cut-outs or re-operations.

Orthopaedic related complications are generally rare (67,69). Moreover, all surgeons in this study were experienced trauma surgeons and well familiar with both procedures. A full scale trial, with a larger sample, will be more likely to reveal the real incidence of complications than the current feasibility study with a small sample.

9.5.10 Complications and mortality in demented patients

The retrospective study in patients with dementia revealed that in total 84 out of the 213 (39.4%) patients developed at least one complication. In comparison, 13 out the 21 (61.9%) recruited patients with dementia had at least one complication (1 patient was excluded because they had a different type of fracture and received a long nail).

The difference in the percentage of complications between the two cohorts most likely was due to the different sample sizes (213 vs 21 patients). Both cohorts were treated in the same period and in the same hospital by the same clinicians and therefore all patients received the same hospital care.

Moreover, the retrospective study revealed a higher number of surgical related complications than the clinical trial. This is most likely attributable to the larger sample size.

Mortality was similar between the retrospective study cohort and the clinical trial cohort (in-hospital: 11.7% vs 16.7% respectively, 1 year: 47.4% vs 50%).

Table 36: Nail vs DHS: operative details, LOS, pain and mortality results.

| | Treatments compared | Surgery results (nail vs DHS) | LOS (days) (nail vs DHS) | Pain (nail vs DHS) | Mortality (nail vs DHS) |
|---------------------|----------------------------------|---|--------------------------|--|--|
| PET | EBA ² vs DHS | Op time: 46.2 vs 48.9min Blood loss: 77 vs 110.8ml Blood trans: 44.8% vs 46.4% | 21 vs 22 | NRS: 1M: 5 vs 7 3M: 4 vs 2 Morphine req: 72.3 vs 91mg | In hospital: 9.7% vs 3.4% 3M: 12.9% vs 6.9% 12M: 28.6% vs 21.4% |
| Yu 2016 | PFNA Vs DHS | NA | NA | NA | Overall: 0% vs 0.9% |
| Sander 2016 | InterTAN Vs SHS | NA | 12 vs 10 | NA | In hospital: 4.8% vs 5.5% 12M: 22.2% vs 24.6% |
| Reindl 2015 | InterTAN/ TFN/Gamma Vs DHS | NA | NA | NA | 12M: 11.6% vs 5.4% |
| Zehir 2015 | PFNA vs DHS | Op time: 44.4 vs 56.9min* Blood loss: 139.7 vs 303.1ml* | 7.2 vs 8.6* | NA | In hospital: 2.1% vs 4.9% 12M: 10.8% vs 10.3% |
| Aktseli 2014 | Gamma vs AMBI SHS | Op time: 45.7 vs 75.5min* | 16.6 vs 16.4 | NA | 12M: 10% vs 12.5% |
| Matre 2013 | InterTAN vs SHS | Op time: no diff Blood loss: 183 vs 263ml* Blood transf: 43% vs 52% | No diff | VAS: 3M: 25 vs 25 12M: 17 vs 17 | In hospital: 2.3% vs 4.1% 12M: 24.6% vs 25.4% |
| Parker 2012 | Targon Vs SHS | Op time: 49 vs 46min* Blood transf: 33% vs 33% | 17.9 vs 16.4 | VAS: 6w: 2.7 vs 2.9 Charnley: 12M: 1.6 vs 1.8 | 12M: 27.7% vs 27% |
| Barton 2010 | Gamma vs SHS | Blood transf: 51% vs 42% | 32 vs 31 | NA | In hospital: 21% vs 10% 12M: 32% vs 22%* |
| Veretta 2010 | (Gamma/ Endovis) vs DHS | Op time: 42 vs 45min Blood loss: 150 vs 200ml | 10.2 vs 10.3 | VAS: 1-5 days: 4.6 vs 4.8 6-10 days: 2.7 vs 2.8 | In hospital: 1.7% vs 1.7% |
| Xu et 2010 | PFNA vs DHS | Op time: 68.5 vs 56.5min* Blood loss: 220.4 vs 472.9ml* Blood transf: 37.2% vs 87.3%* | 7 vs 7.4 | NA | 3M: 2% vs 3.6% 12M: 3.9% vs 5.5% |
| Utrilla 2005 | Gamma vs SHS | Op time: 46 vs 44 min Blood transf: 26.2% vs 40.7%* | NA | NA | In hospital: 6.7% vs 9.4% 12M: 18.3% vs 19.8% |
| Saudan 2002 | PFN vs DHS | Op time: 64 vs 65min Blood transf: 55% vs 67.9% | No diff | Pain (scale 1-4): 12M: 1.36 vs 1.31 | In hospital: 4% vs 3.8% 12M: 16% vs 12.3% |

*indicates statistical significance, no diff: no difference

PET: Pertrochanteric Endovis Trial, Op time: operative time, Blood trans: blood transfusion, morphine req: morphine equivalent requirements

Table 37: Nail vs DHS: PROMS and radiographic results.

| | Treatments compared | Functional outcomes (nail vs DHS) | | Radiographic results (nail vs DHS) | |
|----------------------|----------------------------------|---|--|--|---|
| PET | EBA ² vs DHS | LEM: 3M: 62.4 vs 54.2 TUG 3M: 37.5 vs 31sec | DEMQOL (carer): 3M: 95 (98.5) vs 85 (86) | TAD: 17.73 vs 14.94mm Neck-shaft angle: 126.8° vs 133.6° | Loss of neck length: 0.19 vs 0.23 cm |
| Yu 2016 | PFNA vs DHS | HHS: 12M: 88.24 vs 87.25* 48M: 88.55 vs 86.02* | | Complication rate: 16.4% vs 34.8* | Re-operations: 12M: 0% vs 5.4%* 48M: 4.5% vs 12.5%* |
| Sanders 2016 | InterTAN vs SHS | FIM: 3M: 105.6 vs 103.9 12M: 107.3 vs 108.1 LEM: 3M: 58.3 vs 58.2 12M: 63.1 vs 63.4 | TUG: 3M: 22vs20.5sec 12M: 18vs 17sec 2MWT: 3M: 56m vs 61m 12M: 64m vs 70m | TAD: higher in the nail group* >25mm: 13% vs 6% Re-operations: 10.6% vs 7.1% | Union: 12m: 85% vs 69%* Shortening: >1cm: 17% vs 43%* |
| Reindl 2015 | InterTAN/ TFN/Gamma Vs DHS | LEM: 3M: 56 vs 55.4 12M: 66 vs 64.4 2MWT: 3M: 62m vs 71m 12M: 80m vs 81m | TUG: 3M: 26 vs 26sec 12M: 19 vs 20sec FIM: 3M: 99 vs 106 12M: 106 vs 111 | TAD: 17mm vs 18mm | Loss of neck length: 0.2cm vs 1.0cm* |
| Zehir 2015 | PFNA vs DHS | Walking ability: 6M: 66.7% vs 66.7% | Unrestricted walking: 6M: 55.2% vs 28.4%* | TAD: 22.7 vs 24.02 | Cut-out: 7.3% vs 7.8% Femoral shortening; 5-10mm: 14% vs 56%* |
| Aktselis 2014 | Gamma vs AMBI SHS | Barthel index: 4w: 59.6 vs 52.6 3M: 73.6 vs 70.7 12M: 89.7 vs 81.1* Parker Mobility score: 4w: 2.8 vs 2.1 3M: 4.6 vs 3.8 12M: 6.5 vs 5.7 | EQ-5D 4w: 0.66 vs 0.59 3M: 0.76 vs 0.72 12M: 0.90vs 0.78* | No cut-outs or reoperations | All fractures healed |
| Matre 2013 | InterTAN vs SHS | TUG: 3M: 29 vs 29sec 12M: 27 vs 25 sec EQ-5D: 3M: No diff 12M: No diff | HHS: 3M: no diff 12M: No diff | Neck-shaft angle: 131° vs 138° * Medialisation: >5mm: more frequent in DHS* | TAD: 18mm vs 21mm* Reoperations: 8.2% vs 7.9% |
| Parker 2012 | Targon vs SHS | Parker Mobility score; Statistically significant lower in the DHS after 9 months | | NA | |
| Barton 2010 | Gamma vs SHS | EQ-5D: 12M: 0.37 vs 0.46 | Change in mobility: 1.83 vs 1.49 | TAD > 25mm: 8% vs 9% | Reoperations: 3% vs 2% |
| Veretta 2010 | Gamma/ Endovis vs DHS | NA | | NA | |
| Xu et 2010 | PFNA vs DHS | Mobility score: 5.6 vs 4.4* | | Shortening: 2.6 vs 4.8mm* | Complications: 38.2% vs 29.4% |

| | | | | |
|---|-----------------|------------------------------------|-------------------------------|---|
| Utrilla 2005 | Gamma vs SHS | Mobility score: 12M: 6.4 vs 6.2 | Shortening: 4.5 vs 3.2 | All fractures united Reoperations: 1.2% vs 4.9% |
| Saudan 2002 | PFN vs DHS | Mobility score: 4.94 vs 5.07 | Reoperations: 7.6% vs 2.2% | |
| * indicates statistical significance, no diff: no difference) | | | | |
| PET: Pertrochanteric Endovis Trial | | | | |

9.6 Study limitations

This study had the following limitations:

1. As other studies on hip fractures, there was high level of attrition due to deaths. Attrition was worse in the AMTS<8 group. High attrition resulted in high rate of missing data in key variables and in some cases comparisons between the subgroups were not possible due to the small numbers. Moreover, high attrition has a negative effect on initial sample calculation and as a result treatment effect difference is more difficult to become apparent.
2. This was an intervention trial, and it is impossible to blind the operating surgeon of the randomised group. Moreover, although the patients were not told of their randomised group, they were able to guess their randomisation group by the number of scars they had (3 scars in the nail group vs one scar in the DHS group). However, assessment of the TUG test was performed by health care professionals who were blinded of the randomisation group.
3. This was a feasibility study and as such the sample size was relatively small. As a feasibility study, the primary objective was to assess whether a future definite study can be done and how it can be done. Although this was a feasibility study, it was attempted to assess effectiveness and efficacy of the studied interventions; however, comparisons were not always possible due to the small number of participants. This was unavoidable, due the type of the study. A future full trial study will be more appropriate to assess effectiveness and efficacy of the compared interventions.
4. Similarly, because this study was a feasibility study, the follow up period was relatively short. This may have been a reason why no differences between the groups were seen in terms of PROMS or surgical complications. A future definite trial with a longer follow up should be able to assess outcome measures in later stages.
5. Blood loss results may have been affected by baseline imbalances and by the method blood loss was recorded; we recorded the blood loss separately in the suction tube and the blood loss in the swabs used. Ideally, blood loss will need to be the sum of blood loss in the suction tube and in the surgical swabs used. The method to capture this will need to be determined.

9.7 Final conclusion

This study proved that it is feasible to conduct a randomised control trial including patients with cognitive impairment. However, the following issues were identified:

1. Further work is required in the identification of the optimal primary assessment measure. The Timed Up and Go test which was used in the current study was not a good assessment tool. Not all patients were able to perform the test even at 3 months, and the results varied significantly any comparisons were difficult to be made.
2. Due to the high rate of attrition, especially in the AMTS<8 group, primary outcomes will need to be assessed earlier than later.
3. There was preliminary proof of concept of a treatment effect for the level of pain in the early postoperative period and for the radiographic outcomes at all time points in favour of the nail group.
4. With regards the functional outcomes and quality of life scores (i.e. LEM, LHS, and DEMQOL), no differences between the groups were identified. Similarly, no differences were identified for the surgery related outcomes (i.e. duration of surgery, blood loss, blood transfusion requirements).

In conclusion, a full-scale superiority trial comparing fixation of unstable pertrochanteric fractures between intramedullary and extramedullary fixation is possible, with the following changes in the study design:

- Both patients with and without dementia will be included, but long-term secondary outcomes will be assessed only in patients without dementia.
- The method of assessing blood loss will need to be re-considered; it will have to combine blood loss in the suction and in the surgical swabs (i.e. total blood loss).
- A suitable PROM for quality of life and functional mobility that can be used in both patients with and without dementia can be used as a primary outcome measure; further work is required to identify this tool.
- If a physical assessment tool is to be used, this should be a relatively easy test to perform; patients with hip fractures are very frail patients with pre-existing morbidities and mobility problems.
- Analgesia requirements within the first 2 weeks could be a potentially good variable to assess postoperative pain; for patients with AMTS \geq 8 pain NRS is also a good assessment tool.

- Radiographic outcomes may include TAD, neck collapse, leg shortening, and medialisation; the first radiograph will need to be assessed the next day from surgery. In order to scale the X-rays, the full length of the screw or the barrel plate will need to be measured.
- Re-operations and metalwork complications will need to be secondary late outcomes.
- Cost-effective analysis may reveal a benefit of one treatment over the other.

9.8 Future work

This feasibility study was carried out with the purpose to provide new information that can be used to plan a full trial which will compare treatment effects between intramedullary and extramedullary fixation devices for the treatment of A2 type pertrochanteric fractures. However, before a full trial is carried out, the following questions will need to be answered.

Further work is required to assess the feasibility of using other physical outcome measures and patient-reported outcome measures in patients with hip fractures. We found that the TUG test is not suitable for such a trial. Alternative assessment measures have already been discussed.

Further work is required to explore the reasons that delay discharge of the patients from the hospital. The decision depends on different factors for every patient. It is important to be aware of these reasons so that they can be addressed and, eventually, shorter hospital stay can be achieved. In this direction, an audit on exploring postoperative patient's recovery during hospital stay may reveal possible factors that can be improved and shorten hospital stay.

Preliminary estimates of treatment effect in this study but also in other RCTs have showed that there is no difference between the nail and the DHS group with regard to functional mobility outcomes. If this is confirmed by a large-scale trial, it may be worth assessing and comparing the cost-effectiveness of the two implants. Therefore, including health economic variables may reveal an important difference between the two implants which may be adapted by policy makers and change current clinical practice.

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Appendices

Appendix 1: Ethics approval



Health Research Authority

21 June 2016

Email: hra_approval@nhs.net

Professor Peter Giannoudis
 Professor of Trauma and Orthopaedic Surgery
 University of Leeds
 Academic Unit, A Floor, Clarendon Wing
 Leeds General Infirmary
 Great George Street, Leeds, West Yorkshire
 LS1 3EX

Dear Professor Giannoudis

Letter of HRA Approval for a study processed under pre-HRA Approval systems

| | |
|-------------------------|--|
| Study title: | Outcome following Stabilization of fresh unilateral unstable petrochanteric hip fracture with either the Endovis BA2 cephalomedullary nail or the Dynamic Hip screw: A Single Centre, Feasibility Study |
| IRAS project ID: | 167114 |
| REC reference: | 15/YH/0440 |
| Sponsor | University of Leeds |

Thank you for your request to bring the above referenced study under HRA Approval.

I am pleased to confirm that the study has been given **HRA Approval**, on the basis of the document set provided, any clarifications noted in this letter and taking account of reviews and approvals previously conducted and issued.

The extension of HRA Approval to this study on this basis allows the sponsor and NHS organisations to set-up the study in accordance with HRA Approval processes, with decisions on study set-up being taken on the basis of capacity and capability alone.

Participation of NHS Organisations in England

The sponsor should now provide a copy of this letter to participating NHS organisations in England which are being set up in accordance with HRA Approval Processes.

Appendix B provides important information for sponsors and participating NHS organisations in England for arranging and confirming capacity and capability. **Please read *Appendix B* carefully**, in particular the following sections:

- *Participating NHS organisations in England* – this clarifies the types of participating organisations in the study and whether or not all organisations will be undertaking the same activities
- *Confirmation of capacity and capability* - this confirms whether or not each type of participating NHS organisation in England is expected to give formal confirmation of capacity and capability. Where formal confirmation is not expected, the section also provides details on the time limit given to participating organisations to opt out of the study, or request additional time, before their participation is assumed.

It is critical that you involve both the research management function (e.g. R&D office) supporting each organisation and the local research team (where there is one) in setting up your study. Contact details and further information about working with the research management function for each organisation can be accessed from www.hra.nhs.uk/hra-approval.

Appendices

The HRA Approval letter contains the following appendices:

- A – List of documents reviewed during HRA assessment
- B – Summary of HRA assessment

After HRA Approval

In addition to the document, “*After Ethical Review – guidance for sponsors and investigators*”, issued with your REC Favourable Opinion, please note the following:

- HRA Approval applies for the duration of your REC favourable opinion, unless otherwise notified in writing by the HRA.
- Substantial amendments should be submitted directly to the Research Ethics Committee, as detailed in the *After Ethical Review* document. Non-substantial amendments should be submitted for review by the HRA using the form provided on the [HRA website](http://www.hra.nhs.uk), and emailed to hra.amendments@nhs.net.
- The HRA will categorise amendments (substantial and non-substantial) and issue confirmation of continued HRA Approval. Further details can be found on the [HRA website](http://www.hra.nhs.uk).

Scope

HRA Approval provides an approval for research involving patients or staff in NHS organisations in England.

If your study involves NHS organisations in other countries in the UK, please contact the relevant national coordinating functions for support and advice. Further information can be found at <http://www.hra.nhs.uk/resources/applying-for-reviews/nhs-hsc-rd-review/>.

| | |
|-----------------|--------|
| IRAS project ID | 167114 |
|-----------------|--------|

If there are participating non-NHS organisations, local agreement should be obtained in accordance with the procedures of the local participating non-NHS organisation.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please email the HRA at hra.approval@nhs.net. Additionally, one of our staff would be happy to call and discuss your experience of HRA Approval.

HRA Training

We are pleased to welcome researchers and research management staff at our training days – see details at <http://www.hra.nhs.uk/hra-training/>.

Your IRAS project ID is 167114. Please quote this on all correspondence.

Yours sincerely

Isobel Lyle | Senior Assessor

Health Research Authority

HRA, Room 002, TEDCO Business Centre, Health Research Authority, Rolling Mill Rd, Jarrow NE32 3DT

Hra.approval@nhs.net or Isobel.lyle@nhs.net

M: 07827 984549

www.hra.nhs.uk

The HRA is keen to know your views on the service you received – our short feedback form is available [here](#)

Copy to:

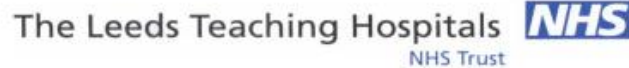
Faculty Research Ethics and Governance, University of Leeds

Ms Anne Gowing, Leeds Teaching Hospitals Trust

LCRN: Yorkshire & Humber

NIHR Portfolio Applications Team

Appendix 2: Patient information sheets



PATIENT INFORMATION SHEET

Outcome following Stabilization of fresh unilateral unstable pertrochanteric hip fracture with either the Endovis BA2 cephalomedullary nail or the Dynamic Hip screw: A Single Centre, Feasibility Study

PET Trial

We would like to invite you to take part in our research study, investigating two different ways of fixing your broken leg. This study will provide us with information which may help improve treatment of patients with similar injuries in the future.

Before you decide to take part we would like you to understand why the research is being done and what it would involve for you. A researcher from our team will go through the information sheet with you and answer any questions you have.

Background information

You have broken (fractured) the upper part of your thigh bone. This part of the bone is called the 'proximal femur' or "hip fracture", see picture below. There are several treatment options for this injury. The vast majority of fractures to the proximal femur require surgery and yours is one of those fractures.



Picture demonstrating a hip fracture

During surgery, the bone is most commonly fixed in place with a metal device which is under the skin. This device can sit inside the hollow part of the proximal femur (a 'nail') or can sit on the surface of the bone (a 'plate').

Why have I been chosen?

You have been chosen as you have suffered a hip fracture and the fracture will require fixation in order to allow you to walk again.

The method of fixation of your fracture can be done either with the pin (nail) method or the plate (hip screw) method. It is expected that 60 patients will take part in this study.

Both plates and nails are successfully used in hospitals throughout the UK for patients with injuries like yours. It is important to know that currently both of these surgical options (plates and nails) are being used in the UK hospitals in everyday clinical practice. None of them is experimental.

However, there is little evidence from research studies to say if one is better than the other. This study will compare plates versus nails. It is important to perform a study in which the two methods are compared, so in the future individuals with similar injuries will receive the best possible treatment.

PART 1 tells you the purpose of this study and what will happen to you if you take part.

PART 2 gives you more detailed information about the conduct of the study.

Ask us if there is anything that is not clear, or if you would like more information. Take time to decide whether or not you wish to take part.

PART 1

1. What is the purpose of the study?

This study aims to determine the best treatment for patients with a fracture of the proximal femur (hip fracture). We are comparing two treatments – nail fixation versus plate fixation. Currently, for these types of injuries based on the clinical examination and the doctor's judgement it is decided which method of fixation to use. The data collected from this study will provide information on whether one method of fixation is better than the other. The results of this study will be used to provide useful information to organise and conduct large-scale future studies. This is why it is called a "pilot" study.

2. Do I have to take part?

It is up to you to decide whether or not to take part. If you decide to take part you will be given this information sheet to keep and be asked to sign a consent form to confirm that you understand what is involved when taking part in this study. If you decide to take part you are free to leave the study at any time and without giving a reason. If you withdraw, unless you object, we will still keep records relating to the treatment given to you, as this is valuable to the study. A decision to withdraw at any time, or a decision not to take part, will not affect the quality of care you receive.

3. What will happen to me if I take part?

You will be allocated to either a nail or plate fixation. The allocation process will be done by a computer and is done purely by chance. There is an equal chance of you receiving either the nail or plate fixation. Your operation will take place adhering to the usual standards that are followed in our hospital.

Following your operation and discharge from the hospital it is normal practice that all patients would be seen and followed up in the hospital outpatient clinic. However, some patients could be followed up by their General Practitioner at one of the appointments (2 weeks). By participating in this study, all your follow up appointments will take place in the trauma and orthopaedic outpatient clinic. During the three hospital appointments that you will be asked to attend, you will be clinically assessed, have x-rays (radiographs) of your hip, asked to fill in three questionnaires and carry out a clinical examination test which is called Time up and Go (TUG) test. This means, that you would have the following extra investigations and examinations that ordinarily you would not have had if you were not part of this research study: a) one clinical and x-ray examination; b) completing the 3 questionnaires; c) carrying out the time up and go test (TUG)

Each questionnaire will take approximately 5 minutes of your time to be completed. The TUG test will take approximately 5 minutes as well.

A. Questionnaires

The three questionnaires that you will complete, they will provide us with the following information:

- Questionnaire 1 will record the severity of pain.
- Questionnaire 2 will record information about your mobility.
- Questionnaire 3 will record information about your quality of life.

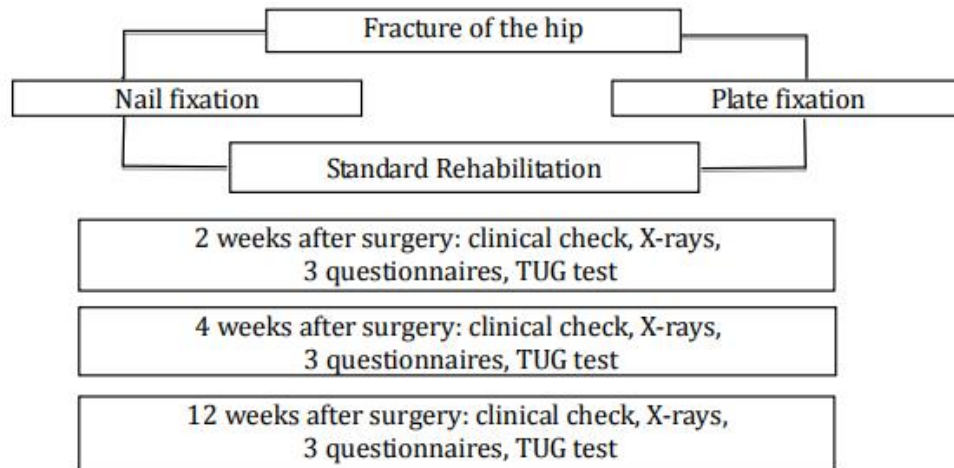
B. TUG Test

The TUG test involves standing up from a seated position, walking three metres, turning around, and then walking three metres back to chair and returning to the seated position. This will also provide us information on your mobility status.

4. What do I have to do?

If you agree to participate in the study you will be seen and assessed at weeks 2, 4, and 12 after the operation in the outpatient clinic. You will be also asked to complete a series of the above mentioned questionnaires and the TUG test during the clinic visits.

In the flow-chart below you can see a schedule of the visits / assessments and what would happen during your participation in the study.



5. What is the procedure that is being tested?

This study is testing whether one method of hip fixation pin (nail) is better than the other plate (hip screw) or whether both are equally effective.

6. What are the alternatives for diagnosis or treatment?

The type of hip fracture you sustained is diagnosed by clinical examination and the radiographs obtained of the affected hip side. Both fixation methods are currently and routinely used for the fixation of hip fractures. These two methods are not experimental. No other alternative method is being used.

7. What are possible disadvantages and risks of taking part?

There are no specific risks of having one type of fixation or the other. Both treatments involve surgery which carries some risks, but the risks are the same and equal to individuals who do not take part.

Risk and complications related to surgical fixation of hip fractures (treated either with a nail or a plate) include but are not limited to the anaesthetic risk, bleeding, risk of deep vein thrombosis (blood clots), damage to the nerves and/or blood vessels, skin breakdown, wound infection, non-union (incomplete healing of the fracture), mal-union (healing of the fracture in a bad position).

If you do decide to take part in the study, you must report any problems you have to your study nurse or doctor. There is also a contact number given at the end of this information sheet for you to phone if you become worried at any time. In the unlikely event of an emergency occurring during the conduct of the study, we may contact your nominated next of kin.

8. What are the possible benefits of taking part?

By participating in this study you will have the advantage to receive a follow up appointment that you may not have had, which involves an extra clinical examination and x-ray providing the surgeon with an earlier assessment of your recovery process.

The information we get from this study will help us improve treatment for future patients with similar fractures.

9. What happens when the research study stops?

The research study will be finished when the last recruited patient will have completed his/her 12 week research clinic visit. The data collected will be analyzed and results obtained will be presented to the academic community. The data will form also the basis for the design of a bigger study in the future.

10. What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak with the researchers who will do their best to answer your question. If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure. Details can be obtained from the hospital.

In the event that something does go wrong and you are harmed during the research study there are no special compensation arrangements. If you are harmed and this is due to someone's negligence then

you may have grounds for a legal action for compensation but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you.

11. Will my taking part in this study be kept confidential?

Yes. All the information about your participation in this study will be kept confidential. The details are included in Part 2.

12. Contact Details

Principal Investigator

Name: Professor Peter Giannoudis Tel. Number: 0113 3922750

Research Nurse

Name: Bernadette Cook Tel. Number: 0113 392 2234/ 07920253864

If your call is urgent and outside of office hours, please call the Principal Investigator Professor Peter Giannoudis Tel: 0113 3922750

This completes Part 1 of the Information Sheet.

If the information in Part 1 has interested you and you are considering participation, please continue to read the additional information in Part 2 before making any decision.

PART 2

13. What if new information becomes available?

Sometimes during the course of a clinical trial, new information becomes available. If this happens, we will tell you about it and discuss with you whether you want to or should continue in the study. If you decide to withdraw, we will make arrangements for your care to continue. If you decide to continue in the study you will be asked to sign an updated consent form.

On receiving new information, we might consider it to be in your best interests to withdraw you from the study. If so, we will explain the reasons and arrange for your care to continue.

If the study is stopped for any other reason, you will be told why and your continuing care will be arranged.

14. What will happen if I don't want to carry on with the study?

If you decide not to carry on with the study, this will not affect the quality of the treatment that you will continue to receive. The Consultant that is responsible for your care would discuss and organise your follow up treatment plan. You may still have the routine follow up appointments in the outpatient clinic

but you will not have to complete the questionnaires. The data collected previously will still be used for analysis of the study results unless you specifically withdraw consent for this. All of your personal information will be kept safe and not be identifiable.

15. Will my part in this study be kept confidential?

If you consent to take part in this study, the records obtained while you are in this study as well as related health records will remain strictly confidential at all times. The information will be held securely on paper and electronically at your treating hospital Leeds General Infirmary under the provisions of the 1998 Data Protection Act. Your name will not be passed to anyone else outside the research team or the sponsor, who is not involved in the trial. You will be allocated a trial number, which will be used as a code to identify you on all trial forms.

All records will have your name removed and will only feature your initials and date of birth. There is the possibility that one of the documents will contain your hospital number, however this will not appear on the same sheet as any clinical results.

During the research study, your medical records will be available to people authorised to work on the trial but may also need to be made available to people authorised by the Research Sponsor, which is the organisation responsible for ensuring that the study is carried out correctly.

The information collected about you may also be shown to authorised people from the UK Regulatory Authority and Independent Ethics Committee; this is to ensure that the study is carried out to the highest possible scientific standards. All will have a duty of confidentiality to you as a research participant.

If you withdraw consent from further study treatment, unless you object, your data will remain on file and will be included in the final study analysis.

At the end of the study, your data will be securely archived for a minimum of 15 years. Arrangements for confidential destruction will then be made.

With your permission, your GP, and other doctors who may be treating you, will be notified that you are taking part in this study.

16. What will happen to the results of this clinical trial?

The results of the study will be available after it finishes and will usually be published in a medical journal or be presented at a scientific conference. The data will be anonymous and none of the patients involved in the trial will be identified in any report or publication.

Should you wish to see the results, or the publication, please ask your study doctor

17. Who is organising and funding this clinical trial?

The trial is organised by the Leeds Institute of Rheumatic and Musculoskeletal Medicine of the University of Leeds under the leadership of Professor Peter Giannoudis. The funding of the study is provided by the Citeiffe- provider of trauma and orthopaedic solutions.

18. Who has reviewed the study?

This study was given favourable ethical opinion for conduct in the NHS by The Yorkshire and Humber Research Ethics Committee.

19. Contact for further information

You are encouraged to ask any questions you wish, before, during or after your treatment. If you have any questions about the study, please speak to your study nurse or doctor, who will be able to provide you with up to date information about the procedure involved. If you wish to read the research on which this study is based, please ask your study nurse or doctor. If you require any further information or have any concerns while taking part in the study please contact the staff listed under section 12.

Alternatively, if you or your relatives have any questions about this study you may wish to contact one of the following organisations that are independent of the hospital at which you are being treated:

The **Patient Advice and Liaison Service**, known as PALS, has been introduced to ensure that the NHS listens to patients, their relatives, carers and friends, and answers their questions and resolves their concerns as quickly as possible. For comments, suggestions or questions, please contact the local **Patient Advice & Liaison Service (PALS)** on tel: **(0113) 206 7168**.

Should you wish to complain about any aspect of your care, please contact the **Patient Relations Department** on tel: **(0113) 206 6261**.

If you decide you would like to take part then please read and sign the consent form. You will be given a copy of this information sheet and the consent form to keep. A copy of the consent form will be filed in your patient notes, one will be filed with the study records.

You can have more time to think this over if you are at all unsure.

Thank you for taking the time to read this information sheet and to consider this study.

PERSONAL CONSULTEE INFORMATION SHEET

Outcome following Stabilization of fresh unilateral unstable pertrochanteric hip fracture with either the Endovis BA2 cephalomedullary nail or the Dynamic Hip screw: A Single Centre, Feasibility Study

PET Trial

We would like to invite your relative/friend to be part of a research study, but your relative/friend is unable to decide for himself/herself whether to participate in this research. To help decide if he/she should join the study we would like to ask you to act as a "Personal Consultee".

This involves considering the wishes of your relative/friend as if they were able to consent for themselves. We are not asking you to give your own opinion or to provide consent on their behalf. We are asking your opinion as to whether or not they would want to be involved.

The patient information sheet that would have been given to the patient if they were able to decide for themselves is incorporated in this information sheet. If the patient has previously stated their views on being involved in research this should be respected.

We will then ask you to consider what you know of *their* wishes and feelings, and to consider *their* interests. If you decide that the patient would have no objection to taking part we will ask you to read and sign this consultee declaration.

Nothing will be done to the relative/friend to which they appear to object. If you have any concerns or you think your relative/friend should be withdrawn from the study please speak with a member of the research team.

You can decide at any point during the study if you feel your relative/friend would no longer wish to be included. If you decide that your relative/friend would not wish to take part it **will not** affect the standard of care they receive in any way.

If you are unsure about taking on the role of consultee you may seek independent advice.

We will understand if you do not want to take on this responsibility.

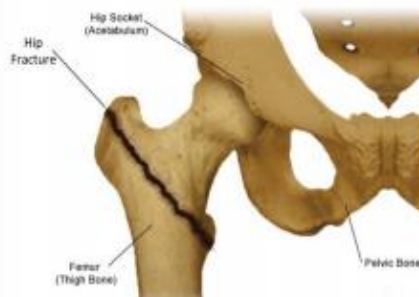
Before you decide if he/she should take part, we would like to give you the following information which is the same as would have been provided to the patient.

Thank you for taking the time to read this.

We would like to invite you to take part in our research study, investigating two different ways of fixing your broken leg. This study will provide us with information which may help improve treatment of patients with similar injuries in the future. Before you decide to take part we would like you to understand why the research is being done and what it would involve for you. A researcher from our team will go through the information sheet with you and answer any questions you have.

Background information

You have broken (fractured) the upper part of your thigh bone. This part of the bone is called the 'proximal femur' or "hip fracture", see picture below. There are several treatment options for this injury. The vast majority of fractures to the proximal femur require surgery and yours is one of those fractures.



Picture demonstrating a hip fracture.

During surgery, the bone is most commonly fixed in place with a metal device which is under the skin. This device can sit inside the hollow part of the proximal femur (a 'nail') or can sit on the surface of the bone (a 'plate').

Why have I been chosen?

You have been chosen as you have suffered a hip fracture and the fracture will require fixation in order to allow you to walk again.

The method of fixation of your fracture can be done either with the pin (nail) method or the plate (hip screw) method. It is expected that 60 patients will take part in this study.

Both plates and nails are successfully used in hospitals throughout the UK for patients with injuries like yours. It is important to know that currently both of these surgical options (plates and nails) are being used in the UK hospitals in everyday clinical practice. None of them is experimental.

However, there is little evidence from research studies to say if one is better than the other. This study will compare plates versus nails. It is important to perform a study in which the two methods are compared, so in the future individuals with similar injuries will receive the best possible treatment.

PART 1 tells you the purpose of this study and what will happen to you if you take part.

PART 2 gives you more detailed information about the conduct of the study.

Ask us if there is anything that is not clear, or if you would like more information. Take time to decide whether or not you wish to take part.

PART 1

1. What is the purpose of the study?

This study aims to determine the best treatment for patients with a fracture of the proximal femur (hip fracture). We are comparing two treatments – nail fixation versus plate fixation. Currently, for these types of injuries based on the clinical examination and the doctor's judgement it is decided which method of fixation to use. The data collected from this study will provide information on whether one method of fixation is better than the other. The results of this study will be used to provide useful information to organise and conduct large-scale future studies. This is why it is called a "pilot

2. Do I have to take part?

It is up to you to decide whether or not to take part. If you decide to take part you will be given this information sheet to keep and be asked to sign a consent form to confirm that you understand what is involved when taking part in this study. If you decide to take part you are free to leave the study at any time and without giving a reason. If you withdraw, unless you object, we will still keep records relating to the treatment given to you, as this is valuable to the study. A decision to withdraw at any time, or a decision not to take part, will not affect the quality of care you receive.

3. What will happen to me if I take part?

You will be allocated to either a nail or plate fixation. The allocation process will be done by a computer and is done purely by chance. There is an equal chance of you receiving either the nail or plate fixation.

Your operation will take place adhering to the usual standards that are followed in our hospital.

Following your operation and discharge from the hospital it is normal practice that all patients would be seen and followed up in the hospital outpatient clinic. However, some patients could be followed up by their General Practitioner at one of the appointments (2 weeks).

By participating in this study, all your follow up appointments will take place in the trauma and orthopaedic outpatient clinic. During the three hospital appointments that you will be asked to attend, you will be clinically assessed, have x-rays (radiographs) of your hip, asked to fill in three questionnaires and carry out a clinical examination test which is called Time up and Go (TUG) test. This means, that you would have the following extra investigations and examinations that ordinarily you would not have had if you were not part of this research study: a) one clinical and x-ray examination; b) completing the 3 questionnaires; c) carrying out the time up and go test (TUG)

Each questionnaire will take approximately 5 minutes of your time to be completed. The TUG test will take approximately 5 minutes as well.

A. Questionnaires

The three questionnaires that you will complete, they will provide us with the following information:

- Questionnaire 1 will record the severity of pain.
- Questionnaire 2 will record information about your mobility.
- Questionnaire 3 will record information about your quality of life.

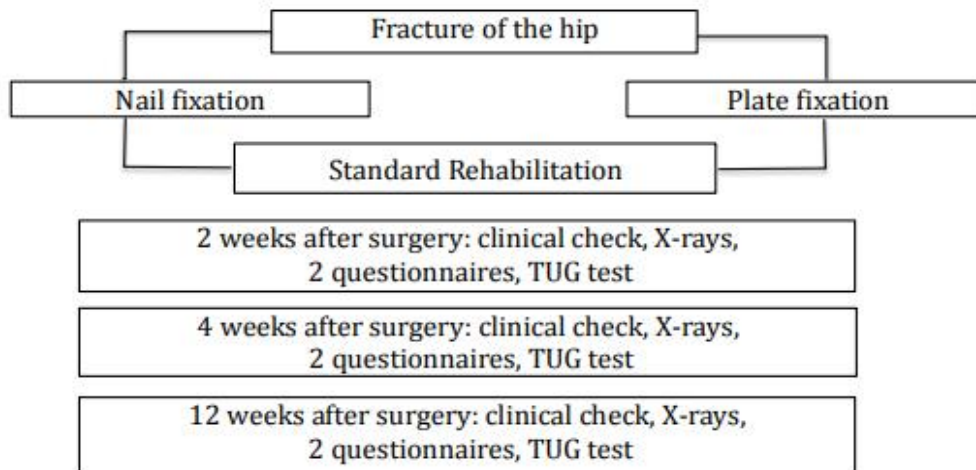
B. TUG Test

The TUG test involves standing up from a seated position, walking three metres, turning around, and then walking three metres back to chair and returning to the seated position. This will also provide us information on your mobility status.

4. What do I have to do?

If you agree to participate in the study you will be seen and assessed at weeks 2, 4, and 12 after the operation in the outpatient clinic. You will be also asked to complete a series of the above mentioned questionnaires and the TUG test during the clinic visits.

In the flow-chart below you can see a schedule of the visits / assessments and what would happen during your participation in the study.



5. What is the procedure that is being tested?

This study is testing whether one method of hip fixation pin (nail) is better than the other plate (hip screw) or whether both are equally effective.

6. What are the alternatives for diagnosis or treatment?

The type of hip fracture you sustained is diagnosed by clinical examination and the radiographs obtained of the affected hip side. Both fixation methods are currently and routinely used for the fixation of hip fractures. These two methods are not experimental. No other alternative method is being used.

7. What are possible disadvantages and risks of taking part?

There are no specific risks of having one type of fixation or the other. Both treatments involve surgery which carries some risks, but the risks are the same and equal to individuals who do not take part.

Risk and complications related to surgical fixation of hip fractures (treated either with a nail or a plate) include but are not limited to the anaesthetic risk, bleeding, risk of deep vein thrombosis (blood clots), damage to the nerves and/or blood vessels, skin breakdown, wound infection, non-union (incomplete healing of the fracture), mal-union (healing of the fracture in a bad position).

If you do decide to take part in the study, you must report any problems you have to your study nurse or doctor. There is also a contact number given at the end of this information sheet for you to phone if you become worried at any time. In the unlikely event of an emergency occurring during the conduct of the study, we may contact your nominated next of kin.

8. What are the possible benefits of taking part?

By participating in this study you will have the advantage to receive a follow up appointment that you may not have had, which involves an extra clinical examination and x-ray providing the surgeon with an earlier assessment of your recovery process.

The information we get from this study will help us improve treatment for future patients with similar fractures.

9. What happens when the research study stops?

The research study will be finished when the last recruited patient will have completed his/her 12 week research clinic visit. The data collected will be analysed and results obtained will be presented to the academic community. The data will form also the basis for the design of a bigger study in the future.

10. What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak with the researchers who will do their best to answer your question. If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure. Details can be obtained from the hospital.

In the event that something does go wrong and you are harmed during the research study there are no special compensation arrangements. If you are harmed and this is due to someone's negligence, then you may have grounds for a legal action for compensation but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you.

11. Will my taking part in this study be kept confidential?

Yes. All the information about your participation in this study will be kept confidential. The details are included in Part 2.

12. Contact Details

Principal Investigator

Name: Professor Peter Giannoudis

Tel. Number: 0113 3922750

Research Nurse

Name: Bernadette Cook

Tel. Number: 0113 392 2234/ 07920253864

If your call is urgent and outside of office hours, please call the Principal Investigator
Professor Peter Giannoudis Tel: 0113 3922750

This completes Part 1 of the Information Sheet.

If the information in Part 1 has interested you and you are considering participation, please continue to read the additional information in Part 2 before making any decision.

PART 2

13. What if new information becomes available?

Sometimes during the course of a clinical trial, new information becomes available. If this happens, we will tell you about it and discuss with you whether you want to or should continue in the study. If you decide to withdraw, we will make arrangements for your care to continue. If you decide to continue in the study you will be asked to sign an updated consent form.

On receiving new information, we might consider it to be in your best interests to withdraw you from the study. If so, we will explain the reasons and arrange for your care to continue.

If the study is stopped for any other reason, you will be told why and your continuing care will be arranged.

14. What will happen if I don't want to carry on with the study?

If you decide not to carry on with the study, this will not affect the quality of the treatment that you will continue to receive. The Consultant that is responsible for your care would discuss and organise your follow up treatment plan. You may still have the routine follow up appointments in the outpatient clinic but you will not have to complete the questionnaires. The data collected previously will still be used for analysis of the study results unless you specifically withdraw consent for this. All of your personal information will be kept safe and not be identifiable.

15. Will my part in this study be kept confidential?

If you consent to take part in this study, the records obtained while you are in this study as well as related health records will remain strictly confidential at all times. The information will be held securely on paper and electronically at your treating hospital Leeds General Infirmary under the provisions of the 1998 Data Protection Act. Your name will not be passed to anyone else outside the research team or the sponsor, who is not involved in the trial. You will be allocated a trial number, which will be used as a code to identify you on all trial forms.

All records will have your name removed and will only feature your initials and date of birth. There is the possibility that one of the documents will contain your hospital number, however this will not appear on the same sheet as any clinical results.

During the research study, your medical records will be available to people authorised to work on the trial but may also need to be made available to people authorised by the Research Sponsor, which is the organisation responsible for ensuring that the study is carried out correctly.

The information collected about you may also be shown to authorised people from the UK Regulatory Authority and Independent Ethics Committee; this is to ensure that the study is carried out to the highest possible scientific standards. All will have a duty of confidentiality to you as a research participant.

If you withdraw consent from further study treatment, unless you object, your data will remain on file and will be included in the final study analysis.

At the end of the study, your data will be securely archived for a minimum of 15 years. Arrangements for confidential destruction will then be made.

With your permission, your GP, and other doctors who may be treating you, will be notified that you are taking part in this study.

16. What will happen to the results of this clinical trial?

The results of the study will be available after it finishes and will usually be published in a medical journal or be presented at a scientific conference. The data will be anonymous and none of the patients involved in the trial will be identified in any report or publication.

Should you wish to see the results, or the publication, please ask your study doctor.

17. Who is organising and funding this clinical trial?

The trial is organised by the Academic Orthopaedic Department of the University of Leeds under the leadership of Professor Peter Giannoudis. The funding of the study is provided by the Cityeffe- provider of trauma and orthopaedic solutions.

18. Who has reviewed the study?

This study was given favourable ethical opinion for conduct in the NHS by The Yorkshire and Humber Research Ethics Committee

19. Contact for further information

You are encouraged to ask any questions you wish, before, during or after your treatment. If you have any questions about the study, please speak to your study nurse or doctor, who will be able to provide you with up to date information about the procedure involved. If you wish to read the research on which this study is based, please ask your study nurse or doctor. If you require any further information or have any concerns while taking part in the study please contact the staff listed under section 12.

Alternatively, if you or your relatives have any questions about this study you may wish to contact one of the following organisations that are independent of the hospital at which you are being treated:

The **Patient Advice and Liaison Service**, known as PALS, has been introduced to ensure that the NHS listens to patients, their relatives, carers and friends, and answers their questions and resolves their concerns as quickly as possible. For comments, suggestions or questions, please contact the local **Patient Advice & Liaison Service (PALS)** on tel: **(0113) 206 7168**.

Should you wish to complain about any aspect of your care, please contact the **Patient Relations Department** on tel: **(0113) 206 6261**.

If you decide you would like to take part then please read and sign the consent form. You will be given a copy of this information sheet and the consent form to keep. A copy of the consent form will be filed in your patient notes, one will be filed with the study records. You can have more time to think this over if you are at all unsure.

Thank you for taking the time to read this information sheet and to consider this study.

NOMINATED CONSULTEE INFORMATION SHEET

Outcome following Stabilization of fresh unilateral unstable pertrochanteric hip fracture with either the Endovis BA2 cephalomedullary nail or the Dynamic Hip screw: A Single Centre, Feasibility Study

PET Trial

We would like to invite you to act as a nominated consultee as attempts to contact a relative or friend to act as personal consultee have been unsuccessful and you have no connection to the research study.

The role of a 'Nominated Consultee' involves considering what the wishes of the patient would be if they were able to consent for themselves. We are asking for your opinion on whether or not they would want to be involved.

The patient information sheet that would have been given to the patient if they were able to decide for themselves is incorporated in this information sheet. If the patient has previously stated their views on being involved in research this should be respected.

We will then ask you to consider what you know of *their* wishes and feelings, and to consider *their* interests. If you decide that the patient would have no objection to taking part we will ask you to read and sign this consultee declaration.

Nothing will be done to the participant to which they appear to object. If you have any concerns or you think the patient should be withdrawn from the study please speak with a member of the research team.

You can decide at any point during the study if you feel the patient would no longer wish to be included. If you decide that the patient would not wish to take part it **will not** affect the standard of care they receive in any way.

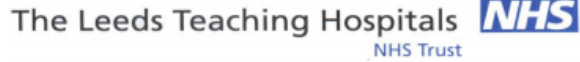
If you are unsure about taking on the role of consultee you may seek independent advice.

We will understand if you do not want to take on this responsibility.

Before you decide if he/she should take part, we would like to give you the following information which is the same as would have been provided to the patient.

Thank you for taking the time to read this.

Appendix 3: Consent forms



PATIENT CONSENT FORM

**Outcome following Stabilization of fresh unilateral unstable pertrochanteric hip fracture with either the Endovis BA2 cephalomedullary nail or the Dynamic Hip screw: A Single Centre, Feasibility Study
PET Trial**

Patient ID: Initials:

Patient initial each point

1. I confirm that I have read and understand the information sheet dated (version) for the above study, and recognize that my hip fracture will be randomized to be treated with either a plate or a nail. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. _____
2. I understand that by participating in this study, all my follow up appointments will take place in the trauma and orthopaedic outpatient clinic. _____
3. During the three hospital appointments that I will be asked to attend I will be clinically assessed, have x-rays (radiographs) of my hip, asked to fill in three questionnaires and carry out a clinical examination, Time up and Go (TUG) test. _____
4. I understand that I would have the following extra investigations and examinations that ordinarily I would not have had if I were not part of this research study: a) one clinical and x-ray examination; b) completing 3 questionnaires; c) carrying out the time up and go test (TUG). _____
5. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. _____
6. I understand that relevant sections of my medical notes and data collected during the study may be looked at by authorised individuals from the Sponsor for the study, UK Regulatory Authority or the Independent Ethics Committee in order to check that the study is being carried out correctly. I give permission, provided, that strict confidentiality is maintained, for these bodies to have access to my medical records for the above study. _____
7. I understand that appropriate personal identifying information will be collected, stored and used by Leeds NHS Trust to enable follow up throughout the duration of the trial. This is on the understanding that any information will be treated with the strictest security and confidentiality. _____
8. I understand that even if I withdraw from the above study, the data collected from me will be used in analysing the results of the study, unless I specifically withdraw consent for this. I understand that my identity will remain anonymous. _____
9. I agree to my GP or any other doctor treating me being informed of my participation in the study. _____
10. I agree to take part in the above study. _____

| | | |
|--------------------------------------|------------------|--------------------------|
| | | |
| Name of the patient | Signature | Date (dd/mm/yyyy) |
| | | |
| Name of person taking consent | Signature | Date (dd/mm/yyyy) |

Original to be retained and filed in the site file. 1 copy to patient, 1 copy to be filed in patient's notes, 1 copy for Sponsor.

PERSONAL CONSULTEE DECLARATION FORM

**Outcome following Stabilization of fresh unilateral unstable pertrochanteric hip fracture with either the Endovis BA2 cephalomedullary nail or the Dynamic Hip screw:
 A Single Centre, Feasibility Study
 PET Trial**

Patient ID: Initials:

Initial each point

1. I confirm that I have read and understand the Personal Consultee Information sheet dated (version ...) for the above study, and recognise that my relative/friend's hip fracture will be randomised to be treated with either a plate or a nail. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily and I believe..... would ordinarily choose to take part in the study. _____
2. I understand that I can request he/she is withdrawn from the study at any time without giving any reason and without his/her care or legal rights being affected. _____
3. I understand that by participating in this study, my relative/friend follow up appointments will take place in the trauma and orthopaedic outpatient clinic. During the three hospital appointments that he/she will be asked to attend, he/she will be clinically assessed, have x-rays (radiographs) of the affected hip, asked to fill in three questionnaires and carry out a clinical examination, Time up and Go (TUG) test. _____
4. I understand that my relative/friend would have the following extra investigations and examinations that ordinarily he/she would not have had if he/she were not part of this research study: a) one clinical and x-ray examination; b) completing 3 questionnaires; c) carrying out the time up and go test (TUG) _____
5. I understand that my relative/friend medical records may be looked at by authorised individuals from the Sponsor for the study, the UK Regulatory Authority or the Independent Ethics Committee in order to check that the study is being carried out correctly. I give permission, provided that strict confidentiality is maintained, for these bodies to have access to my relative/friend's medical records for the above study. _____
6. I understand that even if I withdraw my relative/friend from the study, the data collected for the study will be used in analysing the results of the trial, unless I specifically withdraw my relative/friend for this. I understand that my relative's/friend's identity will remain anonymous. _____
7. I understand that there will be secure storage including electronic, of my relative/friend personal information for the purposes of this study. I understand that any information that could identify them will be kept strictly confidential and that no personal information will be included in the study report or other publication. _____
8. I agree to his/her GP being informed of their participation in the study. _____
9. I agree to being contacted by the research team to keep me fully informed of the trial through my contact details provided below. _____
10. In my opinion the patient would have no objection in taking part in this study. _____

Relationship to patient _____

Name of Personal Consultee **signature** **Date (dd/mm/yyyy)**
 (Please Print)

Name of person taking consent **Signature** **Date (dd/mm/yyyy)**
 (Please Print)

Original to be retained and filed in the site file. 1 copy to patient, 1 copy to be filed in patient's notes, 1 copy for Sponsor.

NOMINATED CONSULTEE DECLARATION FORM

**Outcome following Stabilization of fresh unilateral unstable pertrochanteric hip fracture with either the Endovis BA2 cephalomedullary nail or the Dynamic Hip screw:
 A Single Centre, Feasibility Study
 PET Trial**

Initial each point

Patient ID: Initials:

1. I confirm that I have read and understand the Nominated Consultee information sheet dated (version ...) for the above study and recognise that the patient's hip fracture will be randomised to be treated with either a plate or a nail. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily and I believe..... would ordinarily choose to take part in the study. _____
2. I understand that I can request he/she is withdrawn from the study at any time without giving any reason and without his/her care or legal rights being affected. _____
3. I understand that by participating in this study, the patient's follow up appointments will take place in the trauma and orthopaedic outpatient clinic. During the three hospital appointments that he/she will be asked to attend, he/she will be clinically assessed, have x-rays (radiographs) of the affected hip, asked to fill in three questionnaires and carry out a clinical examination, Time up and Go (TUG) test. _____
4. I understand that the patient would have the following extra investigations and examinations that ordinarily he/she would not have had if he/she were not part of this research study: a) one clinical and x-ray examination; b) completing 3 questionnaires; c) carrying out the time up and go test (TUG) _____
5. I understand that the patient's medical records may be looked at by authorised individuals from the Sponsor for the study, the UK Regulatory Authority or the Independent Ethics Committee in order to check that the study is being carried out correctly. I give permission, provided that strict confidentiality is maintained, for these bodies to have access to the patient's medical records for the above study. _____
6. I understand that even if I withdraw the patient from the study, the data collected for the study will be used in analysing the results of the trial, unless I specifically withdraw the patient for this. I understand that the patient's identity will remain anonymous. _____
7. I understand that there will be secure storage including electronic, of patient's personal information for the purposes of this study. I understand that any information that could identify them will be kept strictly confidential and that no personal information will be included in the study report or other publication. _____
8. I agree to his/her GP being informed of their participation in the study. _____
9. In my opinion the patient would have no objection in taking part in this study. _____

Relationship to patient: _____

 Nominated Consultee (Please print) Signature Date (dd/mm/yyyy)

 Name of person taking consent (Please print) Signature Date
 (dd/mm/yyyy)

Original to be retained and filed in the site file. 1 copy to patient, 1 copy to be filed in patient's notes, 1 copy for Sponsor.

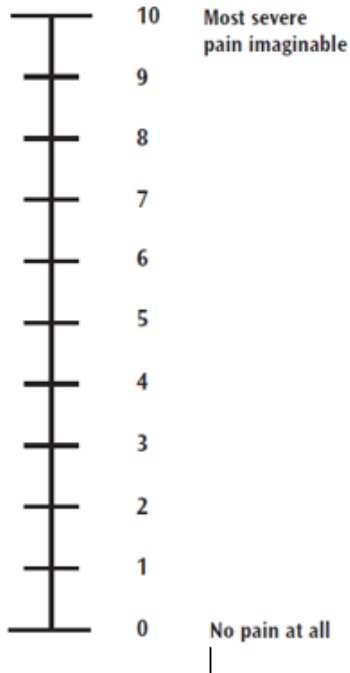
Appendix 4: Pain Numeric Rating Scale

Petrochanteric Endovis Trial (PET)
EudraCT Number: 15/YH/0440

| | |
|-------------------|-------------------------|
| Patient ID: | Patient Initials: |
|-------------------|-------------------------|

| | | | | |
|-------------|----------------------------|----------------------------|----------------------------|-----------------------------|
| Date: | Week | | | |
| | 0 <input type="checkbox"/> | 2 <input type="checkbox"/> | 4 <input type="checkbox"/> | 12 <input type="checkbox"/> |

Pain Numeric Rating Scale



Say to the patient:

- This is a scale to measure pain.
- 0 indicates 'no pain at all'.
- The numbers on the scale indicate increasing levels of pain, up to 10 which is the most severe pain imaginable.
- Which point on the scale shows how much pain you have today?

To the administrator:
In your opinion was the person able to understand this scale?

Yes No

Comment:

Appendix 5: The Lower Extremity Measure

Petrochanteric Endovis Trial (PET)
EudraCT Number: 15/YH0440

Patient's Initials
Study Number ---

| | | | | | | |
|-------------------|-------------------------|-------------|----------------------------|----------------------------|----------------------------|-----------------------------|
| Patient ID: | Patient Initials: | Date: | Week | | | |
| | | | 0 <input type="checkbox"/> | 2 <input type="checkbox"/> | 4 <input type="checkbox"/> | 12 <input type="checkbox"/> |

Lower Extremity Measure

| Question | Level of difficulty | | | | | Task not applicable |
|----------------------------------|-----------------------|-----------------------|-----------------------|------------------------|-----------------------|--------------------------|
| | Impossible to do | Extremely difficult | Moderately difficult | A little bit difficult | Not at all difficult | |
| 1. Getting out of bed is | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="checkbox"/> |
| 2. Getting in/out bathtub is | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="checkbox"/> |
| 3. Getting on/off toilet is | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="checkbox"/> |
| 4. Showering is | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="checkbox"/> |
| 5. Putting on a pair of pants is | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="checkbox"/> |
| 6. Putting on socks/stockings is | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="checkbox"/> |
| 7. Putting on shoes is | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="checkbox"/> |
| 8. Rising from a chair is | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="checkbox"/> |

Petrochanteric Endovis Trial (PET)
EudraCT Number: 15/YH0440

Patient's Initials
Study Number ---

| | | | | | | |
|---|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|--------------------------|
| 9. Standing upright is | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="checkbox"/> |
| 10. Kneeling is | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="checkbox"/> |
| 11. Getting up from kneeling is | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="checkbox"/> |
| 12. Bending to pick something up off the floor is | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="checkbox"/> |
| 13. Sitting is | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="checkbox"/> |
| 14. Walking within the house is | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="checkbox"/> |
| 15. Walking downstairs is | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="checkbox"/> |
| 16. Walking upstairs is | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="checkbox"/> |
| 17. Walking outside is | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="checkbox"/> |
| 18. Walking up/down ramps is | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="checkbox"/> |
| 19. Getting in/out car is | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="checkbox"/> |
| 20. Using public transportation is | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="checkbox"/> |
| 21. Preparing light meals is | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="checkbox"/> |
| 22. Tidying, dusting, washing dishes is | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="checkbox"/> |

Petrochanteric Endovis Trial (PET)
 EudraCT Number: 15/NH/0440

Patient's Initials ---
 Study Number ---

| | | | | | | |
|---|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|--------------------------|
| 23. Doing laundry, vacuuming (heavy housework) is | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="checkbox"/> |
| 24. Gardening/yard work is | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="checkbox"/> |
| 25. Food shopping is | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="checkbox"/> |
| 26. Socializing with friends is | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="checkbox"/> |
| 27. Doing the usual number of hours for your normal daily activities is | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="checkbox"/> |
| 28. Completing your usual daily activities is | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="checkbox"/> |
| 29. Participating in usual leisure activities is | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="checkbox"/> |

Appendix 6: The London Handicap scale

Pertrochanteric Endovis Trial (PET)
EudraCT Number: 15/YH/0440

Patient's Initials ---
Study Number ---

| | | | | | | |
|-------------------|-------------------------|-------------|----------------------------|----------------------------|----------------------------|-----------------------------|
| Patient ID: | Patient Initials: | Date: | Week | | | |
| | | | 0 <input type="checkbox"/> | 2 <input type="checkbox"/> | 4 <input type="checkbox"/> | 12 <input type="checkbox"/> |

London Handicap Scale

Getting around

Think about how you get from one place to another, using any help, aids, or means of transport that you normally have available

Does your health stop you from getting around?

✓ Please tick one box only

Not at all: You go everywhere you want to, no matter how far away.

Very slightly: You go most places you want, but not all.

Quite a lot: You get out of the house, but not far away from it.

Very much: You don't go outside, but you can move around from room to room indoors.

Almost completely: You are confined to a single room, but you can move around in it.

Completely: You are confined to a bed or a chair. You cannot move around at all. There is no-one to move you.

Pertrochanteric Endovis Trial (PET)
EudraCT Number: 15/YH/0440

Patient's Initials ---
Study Number ---

Looking after yourself

Think about things like housework, shopping, looking after money, cooking, laundry getting dressed, washing, shaving, and using the toilet

Does your health stop you looking after yourself?

✓ Please tick one box only

Not at all: You do everything to look after yourself.

Very slightly: You need a little help now and again.

Quite a lot: You need help with some tasks (such as heavy housework or shopping), but no more than once a day.

Very much: You do some things for yourself, but you need help more than once a day. You can be left alone safely for a few hours.

Almost completely: You need help to be available all the time. You cannot be left alone safely.

Completely: You need help with everything. You need constant attention, day and night.

Work and leisure

Think about things like work (paid or not), housework, gardening, sports, hobbies, going out with friends, travelling, reading, looking after children, watching television, and going on holiday

Does your health limit your work or leisure activities?

✓ Please tick one box only

- Not at all: You do everything you want to do.
- Very slightly: You do almost all the things you want to do.
- Quite a lot: You find something to do almost all the time, but you cannot do some things for as long as you would like.
- Very much: You are unable to do a lot of things, but you can find something to do most of the time.
- Almost completely: You are unable to do most things, but you can find something to do some of the time.
- Completely: You sit all day doing nothing. You cannot keep yourself busy or take part in any activities.

Getting on with people

Think about family, friends, and the people you might meet during a normal day

Does your health stop you getting on with people?

✓ Please tick one box only

- Not at all: You get on well with people, see everyone you want to see, and meet new people.
- Very slightly: You get on well with people, but your social life is slightly limited.
- Quite a lot: You are fine with people you know well, but you feel uncomfortable with strangers.
- Very much: You are fine with people you know well but you have few friends and little contact with neighbours. Dealing with strangers is very hard.
- Almost completely: Apart from the people who look after you, you see no-one. You have no friends and no visitors.
- Completely: You don't get on with anyone, not even people who look after you.

Awareness of your surroundings

Think about taking in and understanding the world about you, and finding your way around in it

Does your health stop you understanding the world around you?

✓ Please tick one box only

- Not at all: You fully understand the world around you. You see, hear, speak, and think clearly, and your memory is good.
- Very slightly: You have problems with hearing, speaking, seeing or your memory but these do not stop you doing most things.
- Quite a lot: You have problems with hearing, speaking, seeing or your memory which make life difficult a lot of the time. But, you understand what is going on.
- Very much: You have (he/she has) great difficulty understanding what is going on.
- Almost completely: He/she is unable to tell where he/she is or what day it is. He/she cannot look after him/herself at all.
- Completely: He/she is unconscious, completely unaware of anything going on around him/her.

Affording the things you need

Think about whether health problems have led to any extra expenses, or have caused you to earn less than you would if you were healthy

Are you able to afford the things you need?

✓ Please tick one box only

- Yes, easily: You can afford everything you need. You have easily enough money to buy modern labour saving devices, and anything you may need because of ill health.
- Fairly easily: You have just about enough money. It is fairly easy to cope with expenses caused by ill health.
- Just about: You are less well off than other people like you; however, with sacrifices you can get by without help.
- Not really: You only have enough money to meet your basic needs. You are dependent on state benefits for any extra expenses you have because of ill health.
- No: You are dependent on state benefits, or money from other people or charities. You cannot afford things you need.
- Absolutely not: You have no money at all and no state benefits. You are totally dependent on charity for your most basic needs.

Appendix 7: DEMQOL (patient questionnaire)

Pertrochanteric Endovis Trial (PET)
EudraCT Number: 15/YH/0440

Patient's Initials ---
Study Number

| | | | | | | |
|-------------------|-------------------------|-------------|----------------------------|----------------------------|----------------------------|-----------------------------|
| Patient ID: | Patient Initials: | Date: | Week | | | |
| | | | 0 <input type="checkbox"/> | 2 <input type="checkbox"/> | 4 <input type="checkbox"/> | 12 <input type="checkbox"/> |

DEMQOL (Dementia Quality of Life Measure)

Instructions: Read each of the following questions (in bold) verbatim and show the respondent the response card.

I would like to ask you about your life. There are no right or wrong answers. Just give the answer that best describes how you have felt in the last week. Don't worry if some questions appear not to apply to you. We have to ask the same questions of everybody.

Before we start we'll do a practise question; that's one that doesn't count. (Show the response card and ask respondent to say or point to the answer) In the last week, how much have you enjoyed watching television?

a lot quite a bit a little not at all

Follow up with a prompt question: **Why is that?** or **Tell me a bit more about that.**

DEMQOL

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Pertrochanteric Endovis Trial (PET)
EudraCT Number: 15/YH/0440

Patient's Initials ---
Study Number

For all of the questions I'm going to ask you, I want you to think about the last week.

First I'm going to ask about your feelings. In the last week, have you felt.....

- | | | | | |
|---|--------------------------------|--------------------------------------|-----------------------------------|-------------------------------------|
| 1. cheerful?* | <input type="checkbox"/> a lot | <input type="checkbox"/> quite a bit | <input type="checkbox"/> a little | <input type="checkbox"/> not at all |
| 2. worried or anxious? | <input type="checkbox"/> a lot | <input type="checkbox"/> quite a bit | <input type="checkbox"/> a little | <input type="checkbox"/> not at all |
| 3. that you are enjoying life? ** | <input type="checkbox"/> a lot | <input type="checkbox"/> quite a bit | <input type="checkbox"/> a little | <input type="checkbox"/> not at all |
| 4. frustrated? | <input type="checkbox"/> a lot | <input type="checkbox"/> quite a bit | <input type="checkbox"/> a little | <input type="checkbox"/> not at all |
| 5. confident? ** | <input type="checkbox"/> a lot | <input type="checkbox"/> quite a bit | <input type="checkbox"/> a little | <input type="checkbox"/> not at all |
| 6. full of energy? ** | <input type="checkbox"/> a lot | <input type="checkbox"/> quite a bit | <input type="checkbox"/> a little | <input type="checkbox"/> not at all |
| 7. sad? | <input type="checkbox"/> a lot | <input type="checkbox"/> quite a bit | <input type="checkbox"/> a little | <input type="checkbox"/> not at all |
| 8. lonely? | <input type="checkbox"/> a lot | <input type="checkbox"/> quite a bit | <input type="checkbox"/> a little | <input type="checkbox"/> not at all |
| 9. distressed? | <input type="checkbox"/> a lot | <input type="checkbox"/> quite a bit | <input type="checkbox"/> a little | <input type="checkbox"/> not at all |
| 10. lively? ** | <input type="checkbox"/> a lot | <input type="checkbox"/> quite a bit | <input type="checkbox"/> a little | <input type="checkbox"/> not at all |
| 11. irritable? | <input type="checkbox"/> a lot | <input type="checkbox"/> quite a bit | <input type="checkbox"/> a little | <input type="checkbox"/> not at all |
| 12. fed-up? | <input type="checkbox"/> a lot | <input type="checkbox"/> quite a bit | <input type="checkbox"/> a little | <input type="checkbox"/> not at all |
| 13. that there are things that you wanted to do but couldn't? | <input type="checkbox"/> a lot | <input type="checkbox"/> quite a bit | <input type="checkbox"/> a little | <input type="checkbox"/> not at all |

DEMQOL

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Next, I'm going to ask you about your memory. In the last week, how worried have you been about.....

| | | | | |
|---|--------------------------------|--------------------------------------|-----------------------------------|-------------------------------------|
| 14. forgetting things that happened recently? | <input type="checkbox"/> a lot | <input type="checkbox"/> quite a bit | <input type="checkbox"/> a little | <input type="checkbox"/> not at all |
| 15. forgetting who people are? | <input type="checkbox"/> a lot | <input type="checkbox"/> quite a bit | <input type="checkbox"/> a little | <input type="checkbox"/> not at all |
| 16. forgetting what day it is? | <input type="checkbox"/> a lot | <input type="checkbox"/> quite a bit | <input type="checkbox"/> a little | <input type="checkbox"/> not at all |
| 17. your thoughts being muddled? | <input type="checkbox"/> a lot | <input type="checkbox"/> quite a bit | <input type="checkbox"/> a little | <input type="checkbox"/> not at all |
| 18. difficulty making decisions? | <input type="checkbox"/> a lot | <input type="checkbox"/> quite a bit | <input type="checkbox"/> a little | <input type="checkbox"/> not at all |
| 19. poor concentration? | <input type="checkbox"/> a lot | <input type="checkbox"/> quite a bit | <input type="checkbox"/> a little | <input type="checkbox"/> not at all |

Now, I'm going to ask you about your everyday life. In the last week, how worried have you been about.....

| | | | | |
|--|--------------------------------|--------------------------------------|-----------------------------------|-------------------------------------|
| 20. not having enough company? | <input type="checkbox"/> a lot | <input type="checkbox"/> quite a bit | <input type="checkbox"/> a little | <input type="checkbox"/> not at all |
| 21. how you get on with people close to you? | <input type="checkbox"/> a lot | <input type="checkbox"/> quite a bit | <input type="checkbox"/> a little | <input type="checkbox"/> not at all |
| 22. getting the affection that you want? | <input type="checkbox"/> a lot | <input type="checkbox"/> quite a bit | <input type="checkbox"/> a little | <input type="checkbox"/> not at all |
| 23. people not listening to you? | <input type="checkbox"/> a lot | <input type="checkbox"/> quite a bit | <input type="checkbox"/> a little | <input type="checkbox"/> not at all |
| 24. making yourself understood? | <input type="checkbox"/> a lot | <input type="checkbox"/> quite a bit | <input type="checkbox"/> a little | <input type="checkbox"/> not at all |
| 25. getting help when you need it? | <input type="checkbox"/> a lot | <input type="checkbox"/> quite a bit | <input type="checkbox"/> a little | <input type="checkbox"/> not at all |
| 26. getting to the toilet in time? | <input type="checkbox"/> a lot | <input type="checkbox"/> quite a bit | <input type="checkbox"/> a little | <input type="checkbox"/> not at all |
| 27. how you feel in yourself? | <input type="checkbox"/> a lot | <input type="checkbox"/> quite a bit | <input type="checkbox"/> a little | <input type="checkbox"/> not at all |
| 28. your health overall? | <input type="checkbox"/> a lot | <input type="checkbox"/> quite a bit | <input type="checkbox"/> a little | <input type="checkbox"/> not at all |

We've already talked about lots of things: your feelings, memory and everyday life. Thinking about all of these things in the last week, how would you rate.....

| | | | | |
|--------------------------------------|--------------------------------|--------------------------------------|-----------------------------------|-------------------------------------|
| 29. your quality of life overall? ** | <input type="checkbox"/> a lot | <input type="checkbox"/> quite a bit | <input type="checkbox"/> a little | <input type="checkbox"/> not at all |
|--------------------------------------|--------------------------------|--------------------------------------|-----------------------------------|-------------------------------------|

**Items that need to be reversed before scoring

Appendix 8: DEMQOL-carer

Petrocharteric Endovis Trial (PET)
EudraCT Number: 15/YH/0440

Patient's Initials ---
Study Number ---

| | | | | | | |
|-------------------|-------------------------|-------------|----------------------------|----------------------------|----------------------------|-----------------------------|
| Patient ID: | Patient Initials: | Date: | Week | | | |
| | | | 0 <input type="checkbox"/> | 2 <input type="checkbox"/> | 4 <input type="checkbox"/> | 12 <input type="checkbox"/> |

DEMQOL (Dementia Quality of Life Measure)- Carer Version

Instructions: Read each of the following questions (in bold) verbatim and show the respondent the response card.

I would like to ask you about _____ (your relative's) life, as you are the person who knows him/her best. There are no right or wrong answers. Just give the answer that best describes how _____ (your relative) has felt in the last week. If possible try and give the answer that you think _____ (your relative) would give. Don't worry if some questions appear not to apply to _____ (your relative). We have to ask the same questions of everybody.

Before we start we'll do a practise question; that's one that doesn't count. (Show the response card and ask respondent to say or point to the answer) In the last week, how much has _____ (your relative) enjoyed watching television?

a lot quite a bit a little not at all

Follow up with a prompt question: **Why is that?** or **Tell me a bit more about that.**

DEMQOL- Carer Version

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Petrocharteric Endovis Trial (PET)
EudraCT Number: 15/YH/0440

Patient's Initials ---
Study Number ---

For all of the questions I'm going to ask you, I want you to think about the last week.

First I'm going to ask about _____ (your relative's) feelings. In the last week, would you say that (your relative) has felt

- | | | | | |
|---|--------------------------------|--------------------------------------|-----------------------------------|-------------------------------------|
| 1. cheerful? ** | <input type="checkbox"/> a lot | <input type="checkbox"/> quite a bit | <input type="checkbox"/> a little | <input type="checkbox"/> not at all |
| 2. worried or anxious? | <input type="checkbox"/> a lot | <input type="checkbox"/> quite a bit | <input type="checkbox"/> a little | <input type="checkbox"/> not at all |
| 3. frustrated? | <input type="checkbox"/> a lot | <input type="checkbox"/> quite a bit | <input type="checkbox"/> a little | <input type="checkbox"/> not at all |
| 4. full of energy? ** | <input type="checkbox"/> a lot | <input type="checkbox"/> quite a bit | <input type="checkbox"/> a little | <input type="checkbox"/> not at all |
| 5. sad? | <input type="checkbox"/> a lot | <input type="checkbox"/> quite a bit | <input type="checkbox"/> a little | <input type="checkbox"/> not at all |
| 6. content? | <input type="checkbox"/> a lot | <input type="checkbox"/> quite a bit | <input type="checkbox"/> a little | <input type="checkbox"/> not at all |
| 7. distressed? | <input type="checkbox"/> a lot | <input type="checkbox"/> quite a bit | <input type="checkbox"/> a little | <input type="checkbox"/> not at all |
| 8. lively? ** | <input type="checkbox"/> a lot | <input type="checkbox"/> quite a bit | <input type="checkbox"/> a little | <input type="checkbox"/> not at all |
| 9. irritable? | <input type="checkbox"/> a lot | <input type="checkbox"/> quite a bit | <input type="checkbox"/> a little | <input type="checkbox"/> not at all |
| 10. fed-up? | <input type="checkbox"/> a lot | <input type="checkbox"/> quite a bit | <input type="checkbox"/> a little | <input type="checkbox"/> not at all |
| 11. that he/she has things to look forward to? ** | <input type="checkbox"/> a lot | <input type="checkbox"/> quite a bit | <input type="checkbox"/> a little | <input type="checkbox"/> not at all |

DEMQOL- Carer Version

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Version 1.0- 11/08/2015

Next, I'm going to ask you about _____ (your relative's) memory. In the last week, how worried would you say _____ (your relative) has been about

| | | | | |
|--|--------------------------------|--------------------------------------|-----------------------------------|-------------------------------------|
| 12. his/her memory in general? | <input type="checkbox"/> a lot | <input type="checkbox"/> quite a bit | <input type="checkbox"/> a little | <input type="checkbox"/> not at all |
| 13. forgetting things that happened a long time ago? | <input type="checkbox"/> a lot | <input type="checkbox"/> quite a bit | <input type="checkbox"/> a little | <input type="checkbox"/> not at all |
| 14. forgetting things that happened recently? | <input type="checkbox"/> a lot | <input type="checkbox"/> quite a bit | <input type="checkbox"/> a little | <input type="checkbox"/> not at all |
| 15. forgetting people's names? | <input type="checkbox"/> a lot | <input type="checkbox"/> quite a bit | <input type="checkbox"/> a little | <input type="checkbox"/> not at all |
| 16. forgetting where he/she is? | <input type="checkbox"/> a lot | <input type="checkbox"/> quite a bit | <input type="checkbox"/> a little | <input type="checkbox"/> not at all |
| 17. forgetting what day it is? | <input type="checkbox"/> a lot | <input type="checkbox"/> quite a bit | <input type="checkbox"/> a little | <input type="checkbox"/> not at all |
| 18. his/her thoughts being muddled? | <input type="checkbox"/> a lot | <input type="checkbox"/> quite a bit | <input type="checkbox"/> a little | <input type="checkbox"/> not at all |
| 19. difficulty making decisions? | <input type="checkbox"/> a lot | <input type="checkbox"/> quite a bit | <input type="checkbox"/> a little | <input type="checkbox"/> not at all |
| 20. making him/herself understood? | <input type="checkbox"/> a lot | <input type="checkbox"/> quite a bit | <input type="checkbox"/> a little | <input type="checkbox"/> not at all |

Now, I'm going to ask about _____ (your relative's) everyday life. In the last week, how worried would you say _____ (your relative) has been about

| | | | | |
|---|--------------------------------|--------------------------------------|-----------------------------------|-------------------------------------|
| 21. keeping him/herself clean (eg washing and bathing)? | <input type="checkbox"/> a lot | <input type="checkbox"/> quite a bit | <input type="checkbox"/> a little | <input type="checkbox"/> not at all |
| 22. keeping him/herself looking nice? | <input type="checkbox"/> a lot | <input type="checkbox"/> quite a bit | <input type="checkbox"/> a little | <input type="checkbox"/> not at all |
| 23. getting what he/she wants from the shops? | <input type="checkbox"/> a lot | <input type="checkbox"/> quite a bit | <input type="checkbox"/> a little | <input type="checkbox"/> not at all |
| 24. using money to pay for things? | <input type="checkbox"/> a lot | <input type="checkbox"/> quite a bit | <input type="checkbox"/> a little | <input type="checkbox"/> not at all |
| 25. looking after his/her finances? | <input type="checkbox"/> a lot | <input type="checkbox"/> quite a bit | <input type="checkbox"/> a little | <input type="checkbox"/> not at all |
| 26. things taking longer than they used to? | <input type="checkbox"/> a lot | <input type="checkbox"/> quite a bit | <input type="checkbox"/> a little | <input type="checkbox"/> not at all |
| 27. getting in touch with people? | <input type="checkbox"/> a lot | <input type="checkbox"/> quite a bit | <input type="checkbox"/> a little | <input type="checkbox"/> not at all |
| 28. not having enough company? | <input type="checkbox"/> a lot | <input type="checkbox"/> quite a bit | <input type="checkbox"/> a little | <input type="checkbox"/> not at all |
| 29. not being able to help other people? | <input type="checkbox"/> a lot | <input type="checkbox"/> quite a bit | <input type="checkbox"/> a little | <input type="checkbox"/> not at all |
| 30. not playing a useful part in things? | <input type="checkbox"/> a lot | <input type="checkbox"/> quite a bit | <input type="checkbox"/> a little | <input type="checkbox"/> not at all |
| 31. his/her physical health? | <input type="checkbox"/> a lot | <input type="checkbox"/> quite a bit | <input type="checkbox"/> a little | <input type="checkbox"/> not at all |

We've already talked about lots of things: _____ (your relative's) feelings, memory and everyday life. Thinking about all of these things in the last week, how would you say _____ (your relative) would rate ..

| | | | | |
|---|--------------------------------|--------------------------------------|-----------------------------------|-------------------------------------|
| 32. his/her quality of life overall? ** | <input type="checkbox"/> a lot | <input type="checkbox"/> quite a bit | <input type="checkbox"/> a little | <input type="checkbox"/> not at all |
|---|--------------------------------|--------------------------------------|-----------------------------------|-------------------------------------|

** items that need to be reversed before scoring

Appendix 9: Timed Up and Go test instructions

Petrochanteric Endovis Trial (PET)
University of Leeds, Ref: OR15/280

TUG TEST INSTRUCTIONS

Explanation of the test and blinding procedures

- The Timed Up and Go (TEG) test is one of the primary efficacy measures for the PET study.
- All patients have undergone hip fixation, some with a dynamic hip screw and some with an Endovis BA2 nail.
- It's important that you don't know which treatment the patient has had when you administer the TUG test, because this might affect the way you do the test (even if you don't mean for this to happen).
- If you are already aware of the patient's treatment when you do the test, or if you become aware during the test, please continue with the test but make a note on the form that you were not blinded for this test.
- If this happens more than once, or if you have any concerns about the blinding process, then please let one of the study team know.

Instructions for administering the test

1. The patient should be asked to stand up from a seated position, walk three metres, turn around, and then walking three metres back to chair and returning to the seated position.
2. They should be asked to perform the test as fast as they are safely able.
3. All patients should be asked to use a "rollator" walking aid irrespective of the aid they would normally use (if any).
4. No demonstration should be given (to avoid suggesting to the patient the speed at which they 'should' walk).
5. Each patient should be asked to complete the TUG test 3 times; all times should be recorded.
6. If the patient is unable to complete 3 trials, record the details for those trials that were completed.