Reconstruction of distal femoral fractures with fixed-angled or polyaxial technology; a prospective randomised controlled trial.

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The candidate confirms that the work submitted is his own and that appropriate credit has been given where reference has been made to the work of others.

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Abstract

The management of fractures of the distal femur varies depending on the patient's functional demands, fracture pattern, the availability of appropriate implants and the skill-set of the operating surgeon. It is widely accepted that the treatment of these fractures are challenging due to its prevalence amongst the elderly, a group with confounding co-morbidities, a high percentage of joint prosthesis and osteoporosis, which increase the technical demands on the surgeon and the selected implant.

Locking osteosynthesis devices have been shown to provide superior stability to axial loading compared with traditional, unlocked osteosynthesis plate-screw constructs, blade plates and intra-medullary nails.. However, the outcome following fixation with first-generation, fixed-angle, locking plates and the newer, poly-angled locking plates remains obscure.

This prospective multi-centre prospective pilot study was undertaken to investigate this issue. Forty patients with distal femoral fractures were randomised into two locking osteosynthesis device groups, the fixed-angled, Less Invasive Stabilisation System (LISS) group and the multi-angled, POLYAX plate group, in a 1:1 ratio. Operative, functional and radiological outcomes including; operation time, length of hospital stay, radiological union rates, Oxford knee scores and Quality of life measures (EQ-5D) were investigated and analysed within a 12 month follow-up period.

The results showed an overall mortality rate of 12.5%. The rate of fracture union was 72.5 % at 6 months and 77.5% there after, with 3 patients requiring secondary procedures for non-union. One patient in the LISS group and 1 patients in the Polyax group required revision surgery for implant failure.

Statistically analysis of the data showed no significant differences in both primary (fracture union) and secondary outcomes between either plating system.

Based on our findings, we conclude that patient factors and surgical technic carry more weight in determining the outcome of these injuries rather than the choice of locking osteosynthesis implant, be it mono or poly-angled.

Contents

Abbreviations

World Health organisation (WHO)

United Kingdom (U.K)

National Institute for Health and Care Excellence (NICE)

Arbeitsgemeinschaft fuer Osteosynthesefragen (AO)

Orthopaedic Trauma Association (OTA)

Tumour Necrosis factor (TNF)

Interleukin 1(IL 1)

Interleukin 6 (IL6)

Interleukin 10 (IL 10)

Interleukin 12 (IL 12)

Platelet-derived growth factor (PDGF)

Cyclooxygenase 2 (COX-2)

Bone morphogenetic proteins (BMPs)

Transforming growth factor beta (TGF-β)

Insulin-like growth factors (IGFs)

Mesenchymal stem cells (MSCs)

Dual-energy X-ray Absorptiometry (DEXA)

Bone Mineral Density (BMD)

Standard deviation (SD)

Peak bone mass (PBM)

Parathyroid Hormone (PTH)

Hormone replacement therapy (HRT)

Less Invasive Stabilisation System (LISS)

Minimally invasive plate osteosynthesis (MIPO)

Operating room (OR)

Oxford Knee Score (OKS)

Research Ethics Committee (REC)

Clinical Trials Research Unit's (CTRU)

Charlson Comorbidity index (CCI)

Computed tomography (CT)

Anterior-posterior (AP)

Visual Analogue Scale (VAS)

Advanced Trauma life Support (ATLS)

American Society of Anaesthesiologists (ASA)

Trial Master File (TMF)

Clinical Records File (CRF)

Intravenous (IV)

Adverse Device Events (ADE)

Serious Adverse Device Events (SADE)

Open Reduction Internal Fixation (ORIF)

Research and Development (R&D)

Medicines and Healthcare products Regulatory Agency (MHRA).

National Health Service (NHS)

Non Contact Bridging system (NCB ®)

Figures

Tables

Chapter 1

Introduction

1.0 The burden of trauma

Trauma is a major cause of morbidity and mortality in the developed world, especially amongst the younger population, in the first four decades of life. Figures from the World Health organisation (WHO) have quoted up to 1.2 million deaths per year from road traffic collisions. The WHO also predicts that by 2020, major trauma will rank third in the causes of premature death and loss of health from disability (1).

Although major trauma is frequently associated with high-energy injuries mainly affecting the younger and predominantly male population, its impact on the ever-growing elderly population must not be overlooked. It is common knowledge that in the United Kingdom (U.K), we are becoming an ageing population. In 1982, the life expectancy of a newborn boy was 71 years and 76.8 years for a girl. The office of national statistics data from 2010 confirms an increase in the lifespan for both sexes. Boys are now have a life expectancy of 78.1 years and girls 82.1 year, with this trend set to continue (2).

Geriatric trauma, commonly low-energy in nature, is thought to be as much as, if not more, of an insult to the elderly individual, as high-energy trauma is to young adult, due to their poorer physiological condition, the lack of adequate organ reserves, pre-existing systemic medical comorbidities and local factors, such as, poor bone stock and frail soft tissues, all of which contribute to the patients' diminished ability to heal.

In the elderly, distal femoral fractures are a mirror image of its more prevalent, proximal sibling, the fracture of the neck of femur or hip fracture. Although fractures of the neck of femur have a much higher incidence, one may consider both, two ends of a spectrum of the same condition, as they are in close proximity anatomically.

Hip fractures are a major public health issue. With an increasing ageing population, the incidence of this injury is set to increase with time. Currently, about 70,000 to 75,000 hip fractures occur each year and the annual cost for all U.K hip

fracture cases is about £2 billion. The 30 day mortality after a hip fracture is quoted at around 10% and rises up to 33% within 12 months (3).

For these reasons, coupled with national austerity measures, the department of health in conjunction with National Institute for Health and Care Excellence (NICE) have drawn up guidelines for the management of Hip fractures, highlighting a multidisciplinary approach to its management. Parallel guidance on primary and secondary prevention of fragility fractures, by tackling osteoporosis, a condition responsible of the majority of low-energy fractures about the femur, from the proximal to the distal femur, have also been published by NICE(4).

The rest of this chapter will continue by introducing distal femoral fractures as a clinical entity, considering its epidemiology, classification and the available treatment options, whilst touching on the pathophysiology of bone healing and the shift in the management of these complex injuries towards the use of locked plating technologies.

1.1 The bony Skeleton

Bone is the chief scaffold or supporting tissue of the human body. It makes up the structural framework for the attachment of muscles and is essential for normal gait and mobilisation. The bony skeleton also serves as a protective casing for internal organs, such as the heart, brain and lungs, against blunt trauma. Another essential role of bones in the human body is mineral homeostasis and blood cell production.

There are 206 bones in the adult skeleton of various shapes and sizes. Bones can be classified according to their anatomy or structure. Structural classification is sub-divided into microscopic or macroscopic bone.

Microscopically, the first type of bone formed at any site is woven bone or primary bone. Woven bone is immature bone and the collagen fibres are randomly located. Lamellar bone or secondary bone is formed by the remodelling of woven or primary bone. In lamellar bone the collagen fibres are stress oriented. They are organised and run in parallel chains resulting in a stronger and more rigid structure.

Similar to other forms of connective tissues found in the body, bone is composed of cells and an extracellular matrix. Osteoblasts, osteocytes, osteoclasts

and osteoprogenitor cells are the primary cells found in bone tissue. Osteoprogenitor cells are the so-called “stem” cells of bone, as they are a source of new osteoblasts. Osteoblasts are found lining the surface of bone. Their function is to secrete collagen and the organic matrix, osteoid. Osteoblasts are the precursor cells for osteocytes. Osteocytes, bone-forming cells, sit in the calcified matrix and maintain bone tissue. Osteoclasts are large multinucleated cells derived from haemopoetic cells in the bone marrow and are similar to blood monocytes and macrophages. The name osteoclast is derived from the Greek word ‘clast’ meaning to break and this describes the function of the cell. They are integral to the remodelling, growth and repair of bone(5).

The other major component of bone is the extracellular matrix. It is composed of an organic matrix containing, glycosaminoglycans, glycoproteins, proteoglycans, osteocalcin, oseteonectin and collagen fibres. Type I collagen is the most abundant type of collagen found in the human body and makes up 90% of collagen in bone with small amounts of type X collagen also present. About 70% of bone is made up of bone mineral, hydroxyapatite, which gives bone its rigidity. The extracellular matrix(osteoid) calcifies to form bone. An impairment of calcification leads to an abnormally large amount of osteoid tissue than normal, resulting in weak or abnormal bone, which is commonly seen in rickets(5).

Macroscopically, bone may be described as cortical or cancellous bone, both of which have different properties.

Cortical bone is more abundant, making up to 80% of the entire skeleton. It is characterised by a slow turnover rate and a high young’s modulus (stiffer construct), a lower porosity and a lower surface area compared with cancellous bone. Cortical bone is composed of packed osteons or haversian systems, each with a centrally placed haversian or volkman’s canal. The haversian canal connects osteons and contains arterioles, venules, capillaries and nerves. The interstitial lamellae, which is believed to be remnants of inactivated osteons, occupies the region between active osteons.

Cancellous bone or spongy or trabecular bone has a homogenous structure and is located in the epiphysis and metaphysis of long bones. It has a higher turnover rate as it remodels according to the stress acting across the bone. It is 30-90% porous and contains bone marrow, the site of primary haemopoiesis in the human body.

1.2 The Femur

The femur (Figure1), the primary focus of this thesis, is the longest and heaviest bone in the human body, designed to transmit the weight from the pelvis to the tibia during upright activities. The head of the femur projects superior-medially with 12-15 degrees of anteversion to articulate with the acetabulum. The proximal femur consists of a head, which is two-thirds of a sphere and is covered by articular cartilage, except for its central fovea, the point of attachment of the ligamentum teres, a neck and two trochanters. The greater trochanter is positioned lateral to the femoral neck and the lesser trochanter, medial. The neck and the long axis(shaft) of the femur are at an angle of 115-140 degrees, which allows for the large range of movement at the hip joint and are joined by a trochanteric line (6).

The shaft of the femur, which is roughly circular in its medial section, has a slight anterior bow, which leads onto the distal femur. The femur terminates, two rounded condyles, which articulates with the proximal tibia, forming the knee joint. The condyles are trapezoidal in shape, narrower anteriorly and broader posterior, separated by a deep intercondylar notch. The knee joint axis is parallel to the ground and the axis of the distal femur is 7 degrees to the vertical plane. The popliteal artery courses from medial to posterior around 10cm proximal to the knee joint. Its branches supply blood supply to the distal femur and knee joint. Another important structure, in close proximity to the distal femur is the sciatic nerve, which runs directly posterior and divides into the tibia and common peroneal nerves in the region (6).

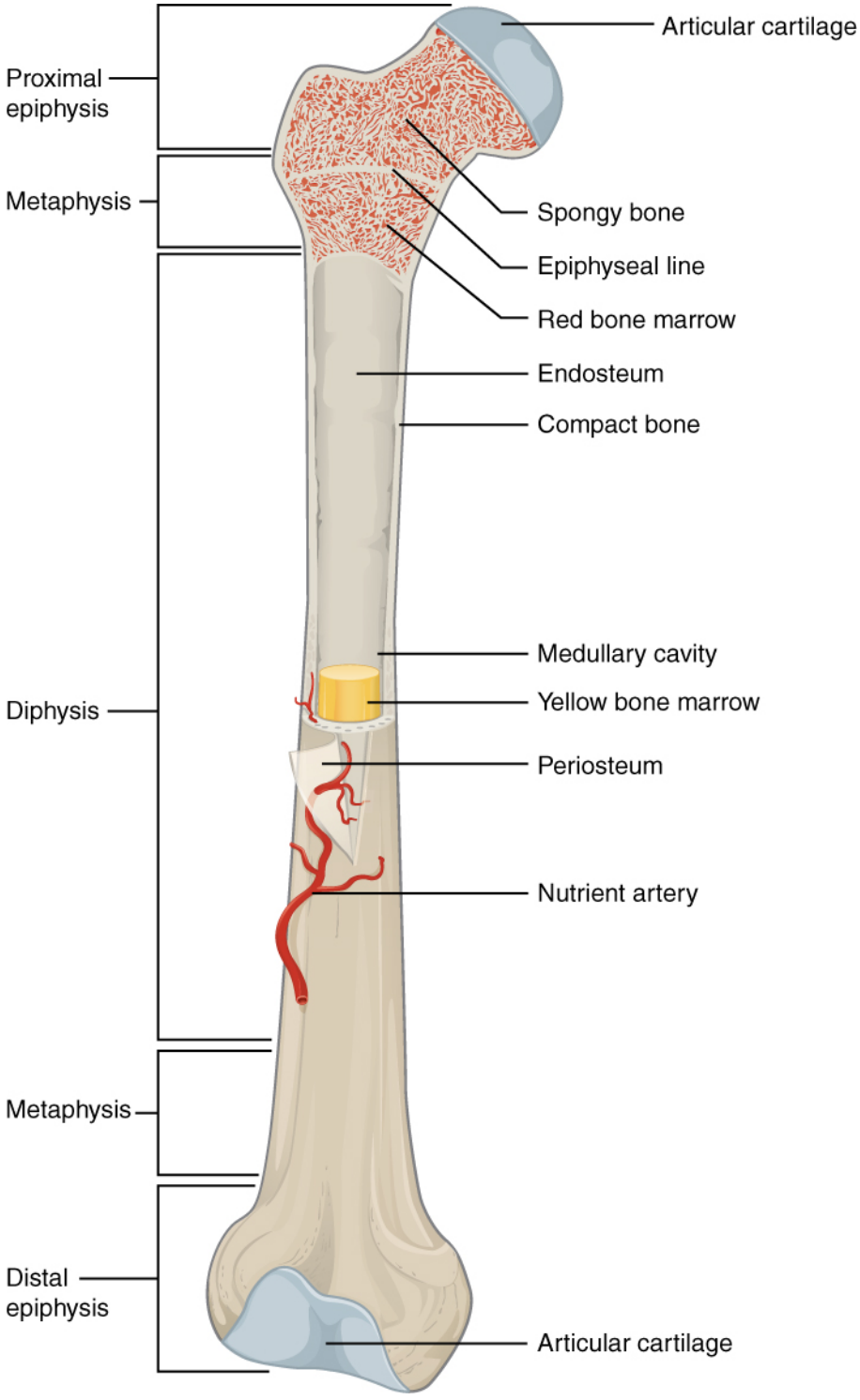


FIGURE 1: THE ADULT FEMUR AND ITS CONSTITUENTS

1.3. Fractures of the distal femur

Fractures of the distal femur are relatively uncommon, accounting for only 6% of femoral fractures, occurring approximately 10 times less frequently than proximal femoral fractures (7). Distal femoral fractures are fractures within the distal 15cm of the femur, which includes the metaphysis, epiphysis and the articular surface. Low energy variants are more common in the elderly, osteoporotic patients, whilst high energy injuries commonly afflict the younger patient, often in the context of polytrauma (7-9). A sub-group of patients, that largely overlap with the elderly, osteoporotic patients, are those sustaining peri-prosthetic distal femoral fractures in close proximity to their total prosthetic knee replacements. Severe functional impairment and permanent disability may result from such injuries, with mal-union and limb shortening and diminishing functional outcome. Non-union with or without infection may also complicate the treatment of distal femoral fractures.

1.3.0 Classification of distal femoral fractures

Distal femoral fractures may be classified descriptively, according to the fracture characteristics. This could be classified as an open or closed injury or depending on the fracture location; supracondylar, condylar or intercondylar. Alternatively, classification could be based on fracture pattern; spiral, oblique or transverse fractures with resulting varus or valgus angulation or rotational deformities. Fractures could also be classified based on articular involvement, as intra-articular or extra-articular fractures. With high-energy injuries, the fracture could be described as segmental, comminuted or oblique with a butterfly fragment.

But in terms of a reproducible classification system, which is robust, encompasses all of the above points and is anatomically based and internationally accepted as a means of communication between various academic institutions, the AO-OTA classification system remains the most acceptable (**Figure 2**) (10). In this classification system, all bones of the body are numerically represented. The distal femur has been assigned the number 33.

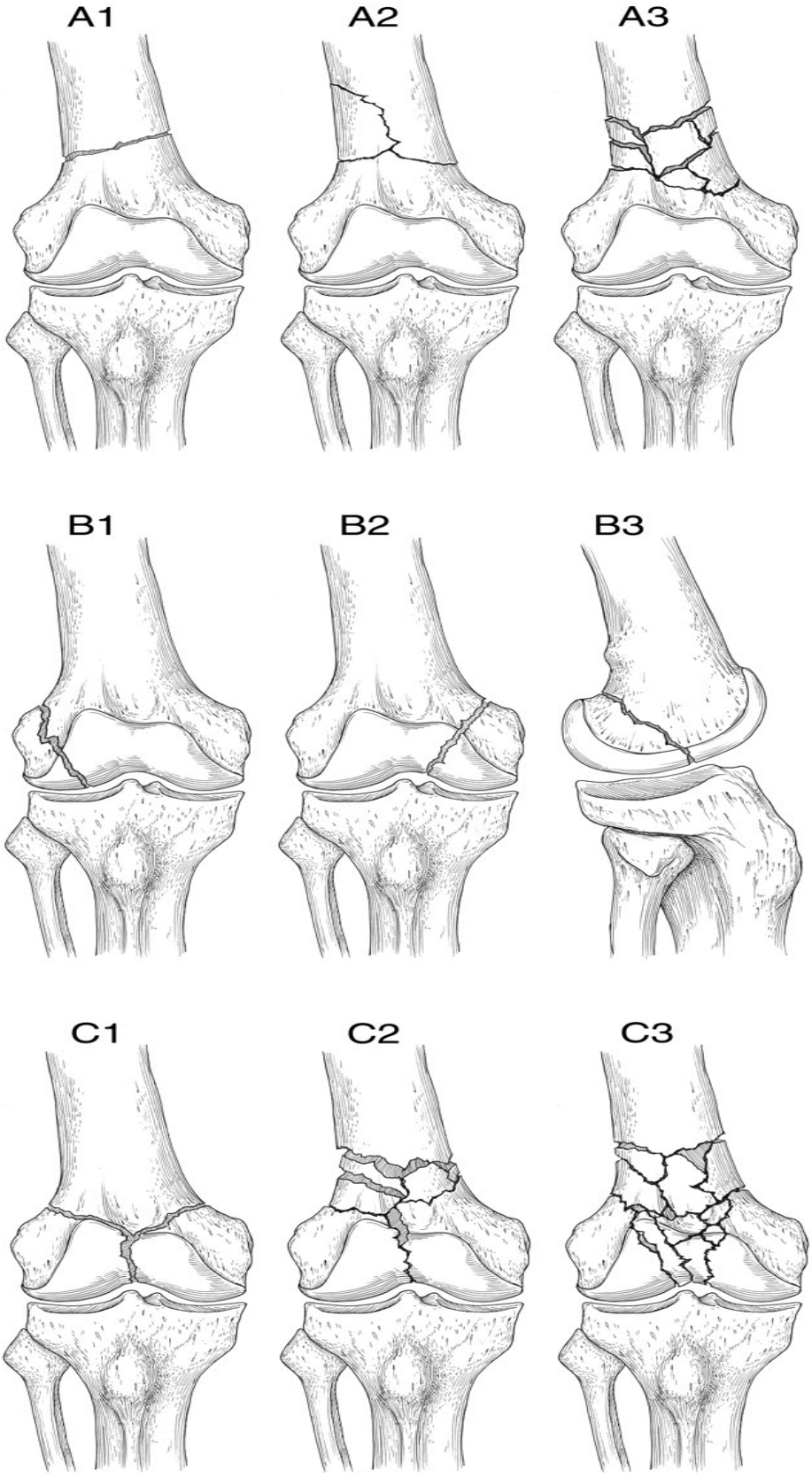


FIGURE 2: AO-OTA CLASSIFICATION OF DISTAL FEMORAL FRACTURES

1.3.1 Periprosthetic fractures of the distal femur

Fractures in proximity to the femoral component of a total hip or knee prosthesis are described as periprosthetic femoral fractures. They occur in 0.1% to 6% of all arthroplasty patients (11-14).

Supracondylar periprosthetic fractures above a total knee replacement are becoming an increasing problem for all orthopaedic and trauma surgeons (15, 16). This is because our elderly population is rising and a large and increasing number of total knee replacements are being performed, increasing the incidence of these relatively rare injuries. The incidence of supracondylar periprosthetic fractures is reported between 0.3% -2.5% (11, 13, 17-26).

Treatment options may be operative or non-operative. Traditional conventional non-operative treatments methods included, bed rest with or without traction and cast immobilisation. The operative fixation methods employed included; Rush rods, supracondylar retrograde nails, compression plates, external fixation frames, with or without bone-grafting and revision arthroplasty with a long-stem prosthesis (13, 17, 27, 28). However, the reported complication rates of these complex fractures range from 19% to 25% (25, 29).

The majority of these injuries occur during minor trauma, frequently after a simple fall or a collapse due to another medical condition . As expected osteoporosis is a principle risk factor for supracondylar periprosthetic fractures. Other factors include; anterior notching of the femoral implant , rheumatoid arthritis , prolonged steroid therapy, female sex and neurological disease (17, 20, 23, 26, 30-32).

More recently the management of periprosthetic femoral fractures has moved towards operative fixation for the majority of cases due to the benefits of early mobilisation, the availability of more sophisticated implants and the high rates of morbidity and possible fatality, associated with prolonged bed rest. Parameters that must be considered in the pre-operative planning for these complex cases includes; the fracture configuration, the functional requirements of the affected patient, the availability of appropriate implants and the patient's bone stock. (12, 25, 33).

1.3.2 Classification of Supracondylar periprosthetic fractures.

Numerous classification systems for Supracondylar periprosthetic fractures after a total knee arthroplasty exist (34), but the most commonly used and widely accepted, due to its ease and its strong correlation with management strategies, was developed by Rorabeck & Taylor (Table 1) and (Figure 3), (17). This classification system takes into account the fracture displacement and the condition of the implant (well fixed or loose prosthesis).

As the aim of treatment for these challenging fractures is to achieve a painless and stable knee joint without significant residual mal-alignment and with maximal functional outcome. The choice of treatment depends on the condition of the knee prosthesis (well fixed or loose), the position and pattern of the fracture, the quality of the residual bone stock, the presence of a proximal implant, the functional demand and the surgical fitness of the patient and his or her ability to tolerate a lengthy invasive procedure.

Generally type I fractures can be treated non-operatively by a period of immobilisation. A cast-brace is preferable to a full cast as it allows monitoring of the soft tissues, which are invariably injured at the time of the index trauma, but also allows range of movement of the knee joint. This prevents stiffness and minimises the morbidity associated with immobilisation such as, deep vein thrombosis and pulmonary emboli. For these groups of patients, restricted weight-bearing and regular radiological assessment must be undertaken during the treatment period to ensure bony alignment is maintained throughout the healing process.

Displaced fractures with an intact prosthesis (type II injuries) should be treated operatively. Several treatment strategies exist for the management of type II injuries. Open reduction and internal fixation, by plating osteosynthesis is one such method, using locking devices. The other is intramedullary nailing , specifically supracondylar retrograde femoral nailing. Both methods have their pros and cons. The operating surgeon must take into account the factors listed above, during the preoperative planning exercise. In addition, the type of knee prosthesis in situ and other patient factors most also be carefully considered, before deciding on the most appropriate method of surgical fixation to be employed. Another issue which must not be overlooked during the preoperative planning stage is the consideration of primary bone grafting.

A supracondylar nail generally interferes less with the soft tissue envelope around the injured distal femur but is contraindicated in very distal fractures, due to the limited fixation in the distal fragment. It is also contraindicated in cases with a pre-existing total hip replacement, as it gives rise to a stress riser between both groups of implants, which invariably predisposes the patient to a further fracture of the already compromised limb.

Locked osteosynthesis technology offers the advantage of providing stable fixation is osteoporotic bone. They are adaptable to different fracture patterns and arthroplasty implants about the knee. In addition they allow unicortical fixation in the proximal femur which is desirable as it allows bridging overlap of a proximal femoral implant in patients with a total hip replacement, preventing a stress riser at the implant junction (15).

The treatment of type III fractures generally consist of a revision arthroplasty using long-stem revision components to bypass the zone of injury. In the most challenging of cases, loose prosthesis are coupled with very poor bone stock or severe fracture comminution rendering the basic revision procedure technical impossible. For such cases a distal femoral prosthesis replacement is required and in most cases a specialist referral is warranted .

Whichever treatment method is applied periprosthetic fractures of the distal femur carry a significant complication risk. Herrera et al published the following; 9% rate of non-union, 4% rate of fixation failure, 3% infection rate and a 13% revision rate (30).

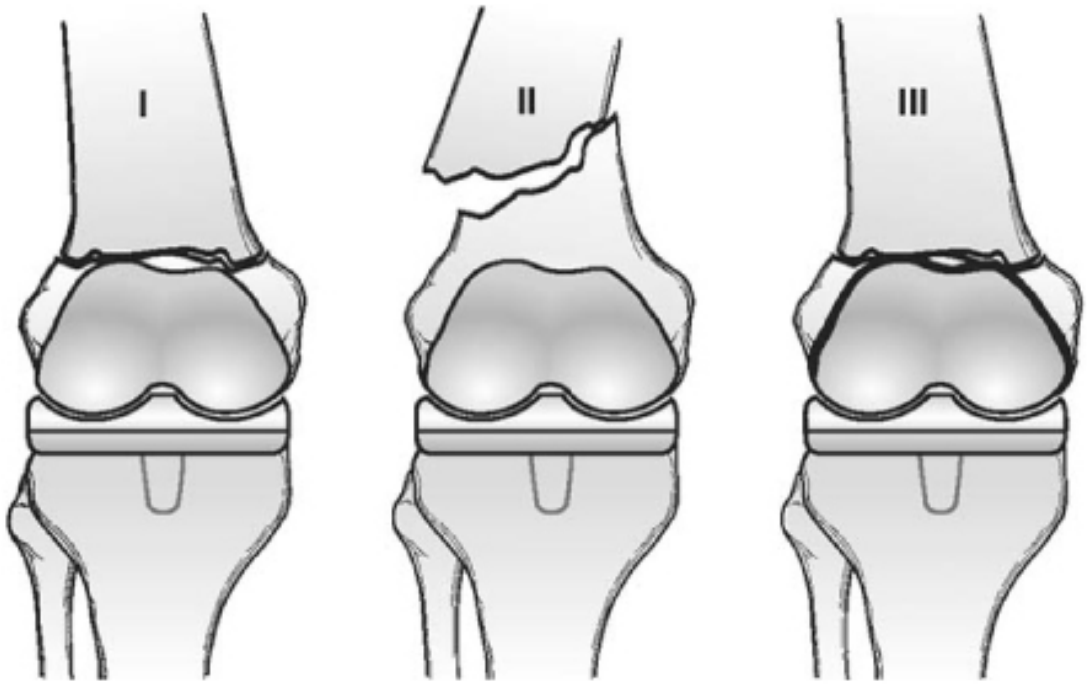


FIGURE 3: RORABECK CLASSIFICATION OF PERIPROSTHETIC FRACTURES OF THE DISTAL FEMUR

Table 1: Rorabeck classification of Periprosthetic fractures of the distal femur

	Rorabeck Classification
Type I	Undisplaced fracture with fixed prosthesis
Type II	Displaced fracture with fixed prosthesis
Type III	Loose prosthesis with undisplaced or displaced fracture

1.4 Patho-physiology of bone injury and healing

A fracture is a break in the structural continuity of a bone. It can also be described in mechanical terms as failure of a bone. Fractures differ in characteristics depending on their location and the vector of the applied force, amongst other factors. The causes of fractures are mainly threefold; trauma, repetitive stress or a pathological process. Fractures are classified as open, if the overlying skin is breached, exposing the fracture site to environmental contaminants or closed in cases where the overlying skin is intact (35).

Fractures due to trauma are caused by a sudden, excessive loading of the bone, either by a direct or indirect force, resulting in failure of the bone. Fractures that result from a direct blow are typically at the point of impact and are usually transverse in nature. Fractures with the so-called “butterfly” fragments occurs after the direct force acts on the long bone over a fulcrum. Both of these fracture patterns are associated with damage to the overlying skin and soft tissues. In cases where a large crushing force is applied a comminuted and displaced fracture results with extensive soft tissue injury (35).

With an indirect force, the bone tends to fail at a distance from the point of force application and soft tissue damage is not inevitable. In reality, most fractures are due to a combination of forces(twisting , compression or tension) and the x-ray pattern reveals the most dominant mechanism. Classically, twisting forces produce a spiral fracture, whilst tension forces produces a transverse fracture pattern (35).

Stress or fatigue fractures occur in normal bone, which is subjected to repetitive cycles of heavy loading. Typically it affects ramblers, athletes, especially long distance runners and military personnel due to their prolonged and demanding regime. The high loads create minute bony deformations, which initiate the normal processes of remodelling, bone resorption and new bone deposition. The repeated and prolonged exposure to stress leads to a state where bone resorption is occurring faster than replacement. At this point, the areas of bone involved are liable to stress fractures. A similar process occurs in individuals whom are on long-term treatment with medications such as, steroids or bisphosphonates, which affects normal bone cell turnover (36).

A pathological fractures occurs when a bone breaks or fails in an area that is weakened by another disease process. The mechanism of injury is usually innocuous, with the fracture occurring as a result of a stress, which does not exceed that required to break healthy bone. Common causes include; osteoporosis, paget's disease and metastatic bone disease (36).

The healing of a fracture is a remarkable and fairly unique process in the body, as in contrast with other tissues, bone heals with no scar tissue and in terms of constituents, it returns almost to its original form. Although fracture healing is divided into stages, in reality the repair or healing of a fracture is a continuous process, with no clear boundaries of the stages described below.

Fracture or bone healing may be classified as primary bone healing or secondary bone healing depending on the degree of fracture stability. The mechanical stability of a fracture, is governed by the mechanical strain at the fracture site. When strain is below 2%, primary bone healing occurs. Secondary bone healing or the so-called "healing by callus" occurs when the strain at the fracture site is between 2% and 10% (37).

Primary bone healing occurs only with absolute stability constructs. An impacted fracture in cancellous bone is one example. Rigid fixation with an osteosynthesis plate is another example, where there is no stimulus for callus formation (38). In such cases, gaps between the fracture surfaces are invaded by new capillaries, closely followed by osteoprogenitor cells, growing in from the edges. Osteoblastic new bone formation occurs directly between the exposed surfaces of fracture fragments. This process is known as gap healing. Lamellar bone is produced to fill narrow spaces of less than 200μm. Larger spaces are first filled by woven bone, which is subsequently remodelled to lamellar bone (37). At around 3-4 weeks after the injury, the fracture is solid enough to allow penetration and bridging of the injured area by bone remodelling units, osteoclastic "cutting cones" followed by osteoblasts.

In contrast, healing by callus or secondary bone healing (Figure 4) occurs via a different route of regeneration. After the index trauma , there is an expected disruption to the tissues, with vessel injury, leading a haematoma formation within the fracture and the surrounding tissues. Bone cells at the facture surfaces

degenerate due to ischaemia. The stages of secondary bone healing are described below:

i. Inflammation and cellular proliferation; The haematoma provides a source of haemopoietic cells, capable of secreting growth factors. Macrophages, neutrophils and platelets release several cytokines (TNF-alpha, IL 1, 6, 10 and 12, PDGF). This acute inflammatory reaction, usually occurs within 8 hours of injury. The inflammatory reaction leads to the initiation of proliferation and differentiation of mesenchymal stem cells from the periosteum, medullary canal and surrounding muscle. Fibroblasts and mesenchymal cells migrate to the fracture site and granulation tissue forms around the fracture ends, as the clot is organised.

ii. Bone repair; The differentiating stem cells provide chrondrogenic and osteogenic cell colonies. Given the right mechanical and biological environment, new bone, callus, is formed. COX-2 mediates the proliferation of osteoblasts and fibroblasts. The cell population around the fracture site now includes osteoclasts, which mops up dead bone and debris. The process continues with the formation of more thick cellular masses of colonies of immature cartilage and bone, which forms the callus, splinting both the endosteal and periosteal surfaces of the fracture. As the immature fibre bone becomes mineralized, movement at the fracture site progressively diminishes. Type II collagen, which is predominantly found in cartilage, is produced early in fracture healing, followed by bony type I collagen. The amount of callus formed at the fracture site is inversely proportional to the extent of immobilization.

iii. Consolidation; bony consolidation continues with continuing osteoclastic and osteoblastic activity the woven bone is transformed into lamellar bone. The bone bridge is now rigid enough to allow osteoclasts to burrow through, clearing debris at the fracture line. Closely followed by osteoblasts, which fill in the remaining gaps between fragments with new bone. This process is slow and depending on the anatomical site and other patient factors, it may take several months before the normal load carrying capacity of the fractured bone is restored.

iv. Remodelling; This process begins in the middle of the repair phase and continues much after clinical bone union has been achieved. Several factors such as, BMPs, TGF-β, IGFs are involved in signalling this phase of bone healing. Newly formed bone (woven bone) is remodelled via organized osteoclastic and osteoblastic

activity, alternating bone resorption and formation. In accordance with Wolff's law, which states that bone remodels according to mechanical stress, thicker lamellae bone is laid down in areas of high stress. Unwanted buttresses are carved away and resorption reforms the medullary canal. Eventually, the anatomy of the bone is restored to its pre-injury state. This is especially true in children, whom have a high capacity of bone growth and regeneration (36).

In both primary and secondary bone healing, certain factors or parameters have to be optimal for this complex healing to occur and a defect in one or more of these factors will predispose the injured long bone to delayed union or extreme cases, non-union. The incidence of femoral non-unions remains a problem for most orthopaedic trauma surgeons and the rate greatly varies depending on several factors including, the type of fixation employed. Long bone non-union rates of 4% were reported with minimally invasive plates, 12% with external fixation and 1.9% after undreamed intramedullary nailing (39-42).

A number of factors affect or influence bone healing, which have been identified from both clinical and experimental laboratory studies. Giannoudis et al highlighted that for a successful bone repair process, four equally important factors most be considered including; adequate mechanical stability, a growth factor (osteoinductive agent), a scaffold (autologous, allogenic or synthetic) and MSCs. This approach, known as "the diamond concept", Figure 5, should always be considered during the management of long bone fractures (43).

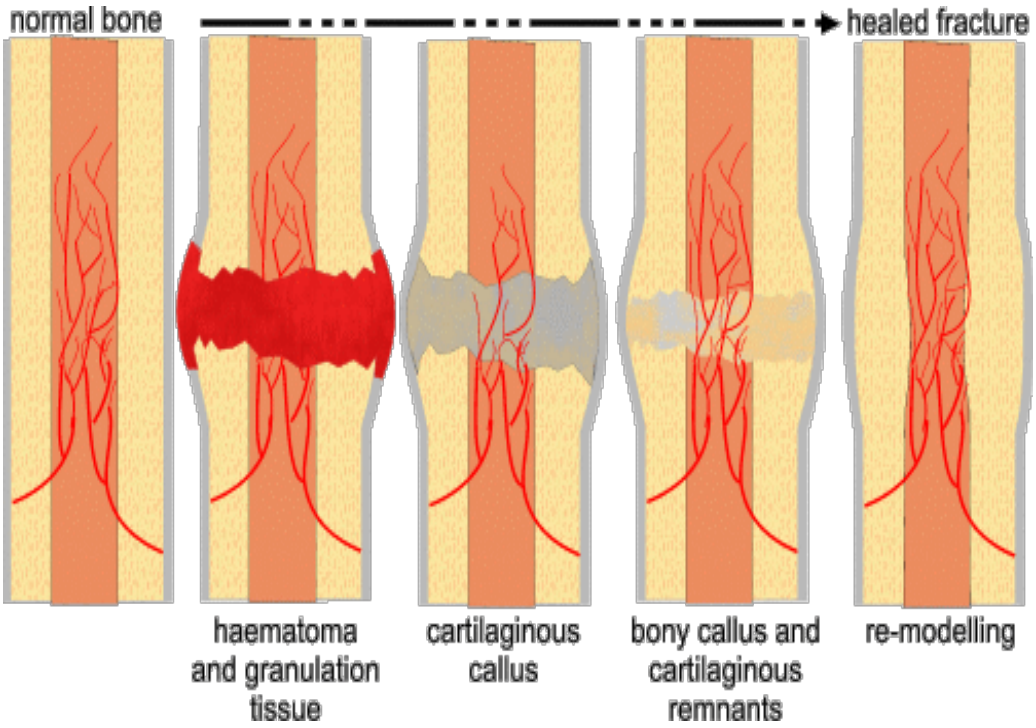


FIGURE 4: STAGES OF BONE INJURY AND REPAIR

(44)

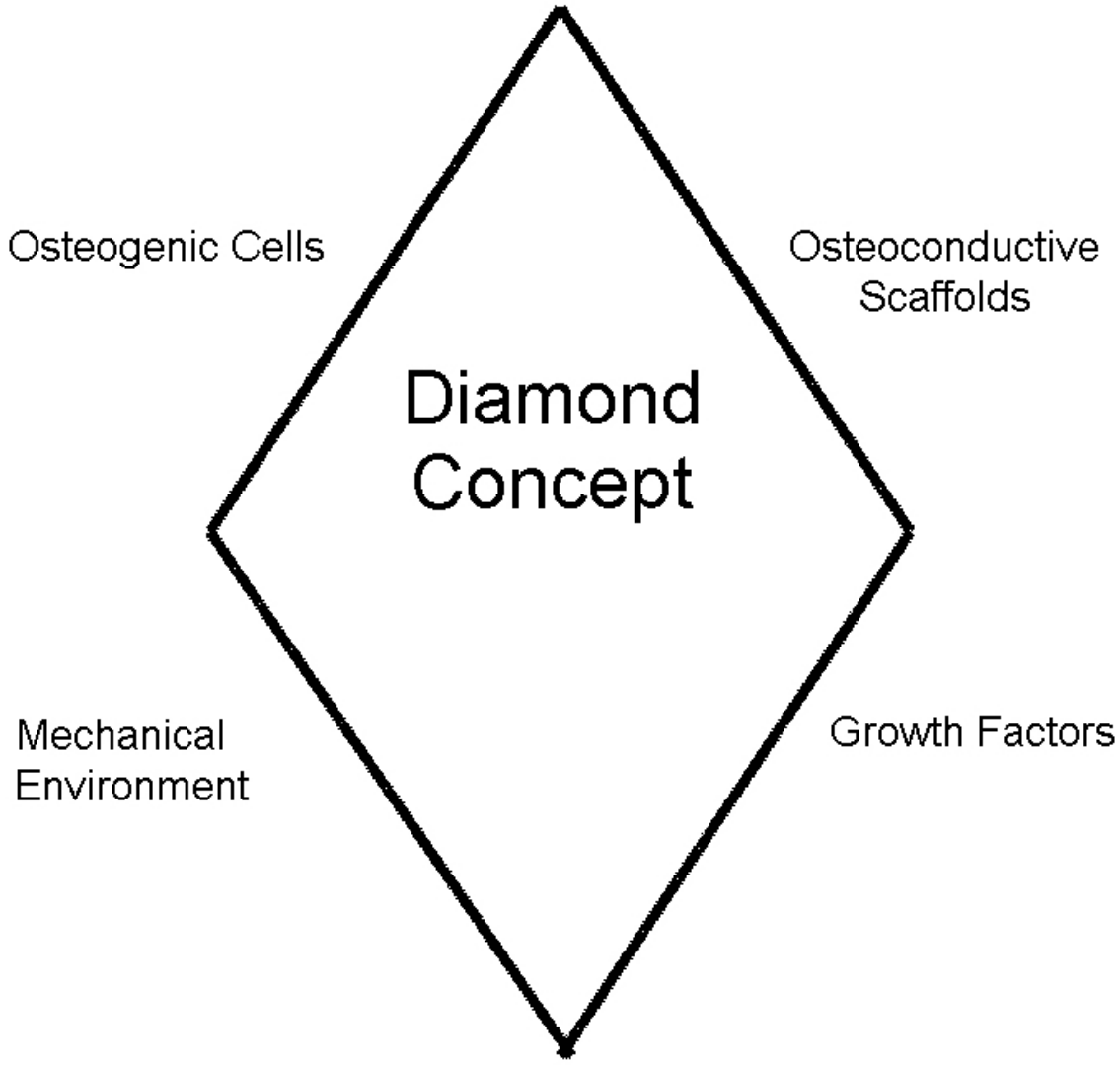


FIGURE 5: THE DIAMOND MODEL OF FRACTURE HEALING

(43)

1.5 The impact of ageing on fracture healing

The physiological process of aging involves complex changes to the human body at a molecular, cellular and systemic level. These changes may lead to functional, social and cognitive degeneration, which may prove difficult to address.

Considering the changes in bone structure and its ability to regenerate, we know that age has an impact on this process. Clinically it is evident that fractures heal and remodel more efficiently and rapidly in children than in adults and that this ability diminishes with increasing age. Osteoporosis, the most clinically relevant change in bone structure which occurs with increasing age, is not mutually-exclusive to the elderly but we know that if an individual lives long enough, they would eventually become osteoporotic.

Several authors have published articles on the negative effect of increasing age on fracture healing (45-49). There is still some controversy around the issue, as most of the laboratory research on this subject has been conducted on rodent models and their conclusions applied to the human population. The observed age-related differences in elderly mice include:

- Longer time to regain normal bone biomechanics.

- Delay in the onset of the periosteal reaction.

- Decreased bone formation.

- Delayed angiogenic invasion of cartilage.

- Protracted period of endochondral ossification.

- Impaired bone remodelling.

The postulated causes of the observed age-related changes at the cellular level include:

- Decreased number and mitotic capacity of mesenchymal progenitor cells.

- Diminished responsiveness of mesenchymal progenitor cells to signalling molecules.

- Decreased blood vessel formation.

- Lower osteoinductive activity of the bone matrix.

- Changes of the local and systemic levels of signalling molecules.

Other postulated factors such as, the reduced capacity of ageing cells to withstand reactive oxidative stresses resulting in cellular damage and in some cases cellular apoptosis may also be implicated (46).

In terms of clinical observations, Robinson et al reported an increased risk of nonunion in non-operatively managed clavicle fractures with advancing age (50). In the same vain, Parker et al considered age as a predictive factor for nonunion after internal fixation of intracapsular fractures of the neck of femur (51).

It is safe to conclude that there is published evidence that increasing age has a negative influence on the healing of fractures. In addition to the reduction in the regenerative capacity of bones with increasing age, other factors such as osteoporosis, complicate the surgical fixation of fractures in the elderly, due to the difficulty of maintaining fracture reduction for a long enough period to allow bony union.

1.6 Osteoporosis

The increasing awareness of osteoporosis and the exponential increase in research on the subject can be attributed to its main consequence, fractures (52). As previously mentioned, the population of the United Kingdom is ageing. The increased longevity and associated increase in oestrogen-deficient years, increases the risk of fragility fractures. Coupled with progressive inactivity, another problem associated with increasing age, fragility or osteoporotic fractures, are now at epidemic proportions. The resulting serious medical, social and financial impact of the disease has brought it to the attention of surgeons, physicians and politicians alike (53-55).

The definition of osteoporosis has altered over the years. Currently the World Health Organisation (WHO) definition for diagnosis is widely accepted not only due to its ease but also for its quantitative value in epidemiology and research studies. A bone density scan or DEXA (Dual-energy X-ray Absorptiometry) is required to measure Bone Mineral Density (BMD).

Osteoporosis is expressed as a T score and is present when the BMD or bone mineral content is more than 2.5 Standard Deviations (S.D) below the Peak Bone

Mass (PBM), (T = <– 2.5 S.D √ PBM). In the case of a fragility fracture, osteoporosis is said to be established or severe. A T score of between -1 and -2.5 below the peak bone mass is classed as osteopenia. Where the BMD is related to age-matched means the S.D difference from the mean is expressed as a Z score (56, 57).

The T-score although widely accepted and used still has its limitations. Faulkner et al published literature on the rate of decline of BMD with age and the striking variation with the anatomical site and the method of measurement of BMD employed (58). Another salient limitation of the T score method is the sole measurement of bone mineral (i.e. calcium), without the consideration of other factors such as, the size, structure and composition of the bone (59, 60). As clinicians, we know the risk factors for fragility fractures in the elderly are multi-factorial and the sole use of T-scores to diagnose osteoporosis would lead to a gross underestimation of the problem.

1.6.0 Osteoporotic fractures

It is common knowledge in medical circles that bone loss is an important risk factor for fractures. This relationship is analogous with for example, the link between obesity and type II diabetes mellitus. Although osteoporosis is a major risk factor for fractures and fractures are the sole important consequence of osteoporosis, the relationship between the two is not as simplistic as it appears, as we know the causes of fractures in the elderly are multifactorial and may reflect a gradual decline in the general health and wellbeing of the affected individual (52).

BMD is inversely related to the fracture rate and in general predicts the likelihood of fractures (61). But not all osteoporotic patients sustain fragility fractures and not all elderly patients with fractures are affected by osteoporosis. This broad inexact relationship between BMD and fractures means that the efficiency of treatment regimes for osteoporosis should consider a reduction in fracture rate as the targeted-point, not an increase in BMD, as BMD measurements are limited by their lack of consideration of the size, structure and composition of the bone, as mentioned above (52).

The structural failure of a bone or a fracture in the elderly is a common problem and it results from the force applied exceeding the deforming strength of the bone. Falls are an important and the primary cause of fractures in this age group. Understanding the causes and reducing their frequency is a vital aspect of fracture management (62, 63). Looking at the risk factors for osteoporotic fractures and those for osteoporosis shows considerable overlap. As expected the risk factors for osteoporotic fractures are more extensive than those for osteoporosis. Table 2 and Table 3 summarises both risk factors.

Table 2: Risk factors for Osteoporosis

Oestrogen deficiency	Premature menopause(<45 years) Prolonged secondary amenorrhoea(>1 year) Primary Hypogonadism
Corticosteroid therapy	Prednisolone 7.5 mg daily for >1 year*
Maternal history of hip fracture	
Low Body Mass Index (BMI <19kg/m^2)	
Associated disorders	Anorexia Nervosa Coeliac disease Thyrotoxicosis Prolonged immobilisation Cushing's disease Primary hyperparathyroidism Transplantation Renal glomerular failure
Other lifestyle factors	Tobacco use Alcohol excess ? caffeine excess

***** *lower amounts of steroids also increase bone loss*

(52)

Table 3: Risk factors for osteoporotic fractures

Female Sex
Premature menopause
Increasing Age
Primary and Secondary Amenorrhoea
Excess Alcohol
High bone turnover
Long-term immobilisation
Vitamin D deficiency
Low dietary calcium intake
Primary and Secondary hypogonadism
Asian or white ethnic origin
Previous fragility fracture
Low Bone Mineral Density
Glucocorticoid therapy
Family history of hip fracture
Poor visual acuity
Low Body weight
Neuromuscular disorders
Cigarette Smoking

(57)

Fractures of the vertebrae, hip, forearm and less commonly the pelvis and distal femur that occur with minimal trauma are generally considered to be related to bone loss and are called insufficiency or fragility fractures, all of which increase in subjects with low bone density (57).

About 30% of fractures in men, 66% of fractures in women and 70% of inpatient fractures are potentially osteoporotic. The distal femur, along with the hip, wrist, spine and pelvis are among the 10 most frequent sites of osteoporotic fractures (64-66).

Iqbal et al describes osteoporosis as a systemic progressive disease affecting mainly the aging population, which is responsible for significant morbidity and mortality due to fractures and their complications (67).

A conservative estimate of the annual cost for the treatment of fragility fractures in the U.K is put at more than £942 million. The majority of this sum is attributed to Hip fracture care and the long-term care of afflicted patients (61). This is reflected in the fact that more than 20% of orthopaedic bed occupancy in the U.K is due to hip fractures and it is estimated that over 20,000 osteoporotic fractures occur every year (68)

The consequences of fragility fractures; increased morbidity and mortality have been well published (68, 69) and this has led to both a social and political drive to educate clinicians and other healthcare professionals to ensure appropriate care for the affected patients. Several guidelines exist for the management of common fragility fractures. The Royal College of physicians published guidelines in 1999 & NICE also published guidelines and updates for the management of hip fractures (4, 61).

All internal fixation devices used in the osteosynthesis of osteoporotic bone must provide adequate purchase on fracture fragments in addition to providing stability in the coronal plane to maintain reduction and alignment during the healing process. Locking plate technologies are most apt to these biomechanical demands (70-75).

1.6.1 Management of osteoporosis: Treatment and Prevention

In simple terms the prevention and treatment of osteoporosis is based on the prevention of bone loss and maximising peak bone mass. By the time a patient is

afflicted with a fragility fracture, it is usually too late to tackle PBM, as osteoporosis is usually advanced by this stage. As mentioned previously a reduction in fragility fractures is the aim of osteoporosis treatment as we know the likelihood of further fractures is considerably greater once the first fracture has occurred.

PBM, the maximum bone mass obtained in early adult life, is a major determinant of bone mass in later life. Understandably, it is influenced by the interaction of genetic and mechanical factors, and also modified by nutritional and hormonal influences. Activities such as regular exercise additional dietary oral calcium and the avoidance of known risk factors such as; excessive alcohol use, immobility and smoking all work towards optimising PBM. Early identification and treatment of endocrine disorders such as, Cushing's syndrome and thyrotoxicosis are also favourable (52).

In terms of medical treatments, hormone replacement therapy (HRT) in peri-menopausal women can be used in prevention by decreasing skeletal bone resorption rate. Other therapies are also based on the principles that the rate of bone loss maybe reduced by increasing bone formation or by inhibiting osteoclastic bone resorption (bone turnover).

Antiresorptive agents, such as bisphosphonates, not only reduce osteoclastic bone resorption and remodelling but also lead to a delay in the decline of osteoblastic activity. Bisphosphonates are frequently prescribed in combination with calcium and vitamin D supplements.

Anabolic agents, such as Parathyroid Hormone (PTH), have a direct anabolic affect on the skeleton via osteoblastic activity. Several studies have reported impressive increase in BMD after daily injections of recombinant PTH (76, 77). The obvious downside to this treatment is the need for daily self-administered injections, which some patients do not tolerate.

Strontium renelate is the most recent addition to the list of therapies for osteoporosis. It is an oral medication which has shown to reduce the risk of vertebral and non-vertebral fractures in high-risk post-menopausal women with osteoporosis (78, 79).

1.6.2 Surgical management of osteoporotic fractures

The management principles of fractures in osteoporotic bone are largely consistent with the management of fractures in bones of normal density. Undisplaced fractures are managed by immobilisation for a period of time, followed by rehabilitation. Operative fixation in osteoporotic bone on the other hand, requires special considerations as osteoporosis influences both the strength and stiffness of bone (35).

A decrease in the stiffness and strength of cortical bone occurs in the region of a few per cent per decade of adult life. This is due to endosteal diaphyseal resorption and medullary expansion in both sexes but to a greater degree in women, as they lack the concurrent bone apposition in the femur and tibia which occurs in men (80).

Changes in cancellous bone structure; a decrease in trabecular thickness, interruption of the trabecular network, a reduction in trabecular number and connectivity, also serve to diminish the strength of cancellous bone in elderly contributing to the reduction of bone mass (81).

We know that bone responds to mechanical stress by altering both its internal and external architecture to meet its physiological demands (Wolff's law). The physical demands of individuals vary greatly according to their occupation, hobbies and so on, thus we expect a variation in individual bone architecture and bone mass. Based on these factors, we expect a frail elderly woman to have decreased bone mass compared to a young elite athlete, as their physical demands are at opposite ends of the spectrum.

Changes in bone architecture have an impact on the strength of fracture fixations. The holding power of bone screws directly correlates to overall bone density, the cortical thickness and the cancellous density. Consequently, fixations in osteoporotic bone have an increased risk of failure due to the decreased amount of both cortical and cancellous bone for screw threads to gain purchase to, hence a decreased pull-out strength of fixed screws (82, 83).

Conventional osteosynthesis devices are load-bearing constructs. The load on the bone is transmitted to the implant distal to the fracture and from the implant back onto the bone, proximal to the fracture. The transfer of load relies on the frictional force at the implant-bone interface, which is generated by the tightening of the bone

screws, an area of high bone strain. If the load transmission at the implant-bone interface exceeds the strain tolerance of the osteoporotic bone, a process of microfracture and bone resorption around the screw holes begins, resulting in loosening of the implant, screw pull out and eventual implant failure.

Osteoporosis is also associated with prolonged fracture healing time. This is supported by research from animal models (84). This observation may be coincidental as osteoporosis is most prevalent amongst the elderly, a group we know to suffer from poor regenerative capacity. The hypothesis' for this observation includes; a fewer number and a lower proliferative response of mesenchymal stem cells in osteoporotic bone and an impaired response of bone cells in osteoporotic patients to mechanical stress (85, 86).

An increased fracture healing time in osteoporotic bone would increase the risk of implant failure, as the strain on the bone screws acts for an extended time period. In normal bone or in paediatric bone, where healing occurs rapidly, the overall strain on the bone screws are significantly attenuated as the healing bone takes on more load carrying responsibilities as healing progresses, eventually rendering the implant void of function.

In cases of prolonged fracture healing time or delayed union, the bone-implant interface is exposed to high strain for a longer period of time, which increases the chance of implant failure. Screw cut out is the common mode of failure in osteoporotic bone, whereas, screw breakage occurs more frequently in bone of normal density, because the load transmitted at the implant-bone interface exceeds the load carrying capacity of the bone screw.

The operative management of osteoporotic bone comes with technical difficulties, resulting from a diminished available cortical and cancellous bone stock for secure implant fixation. Proper pre-operative planning is of paramount importance.

Recommendations to decrease the risk of fixation failure include (71, 81);

- The use of techniques of relative stability (bridge and buttress fixation).

- Selection of devices providing angular stability (locked devices).

- The use of intramedullary or load sharing devices.

- Bone augmentation and grafting in appropriate cases.

- The consideration of arthroplasty for comminuted intra-articular fractures.

1.7 Internal fixation – Plate osteosynthesis

Distal femoral fractures are almost exclusively now treated by operative means currently with great success. Various operative methods are undertaking depending on multiple factors including; injury pattern, patient factors, surgeon preferences and implant availability and costs. It is widely accepted that internal fixation is the gold standard for the treatment of these challenging injuries, especially in the presence of stable arthroplasty components (15, 16, 35).

But this was not always the case. Since the advent of plating of the distal femur in the 1960s, numerous improvements in trauma management, implant design, operative techniques and the use of prophylactic antibiotics have meant that most fractures of the distal femur can be treated by open reduction and internal fixation with reduced complication rates (87, 88). Implants such as the 90° angled blade plate (the condylar plate) and another implant of its era, the Dynamic Condylar Screw have both come in and gone out of fixation fashion.

Another such development which has since been shelved is the Dynamic Compression Plate. This implant was associated reduced healing rates due to the compromise to extramedullary blood flow from periosteal vessel damage secondary to the high contact area of the compression plate on the periosteal surface (89). This in-turn reignited the debate of iatrogenic soft-tissue stripping and the effects of implants on bone vascularity and healing. Following this was the development of Limited Contact Dynamic Compression Plates. These implants have a reduced under surface area of contact to the bone and appears to preserve blood supply.(90)

This brings us to the latest in the line of osteosynthesis devices, the Locking Compression Plate. The unique characteristic of these implants are the threaded screw heads, which locked into the osteosynthesis plate, which allow the maximum transfer of load from the screw neck to the osteosynthesis fixator, creating a fixed angled, axially stable construct (91). These devices do not rely on the friction force generated between a conventional non-locked osteosynthesis fixator and the underlying bone by the tightening of the screws, for the transfer of load. Therefore, with locking plate technology, there is less contact between the two and better preservation of periosteal blood flow, facilitating fracture healing (92).

In these implants screws can be inserted either into one cortex (unicortical) or into both cortices of the femur (bicortical). Unicortical bone screws have lower load carrying capability than bicortical screws. By locking the screws into the plate, a fixed-angle construct is created that is much less prone to loosening or toggle than traditional non-locked plates (93). This locked screw-plate connection provides the path for load transmission to the plate. Due to the historical high complication rates associated with open reduction and internal fixation(ORIF) of these fractures and technological advancement in medical engineering, operative management has moved towards minimally invasive methods of open reduction and internal fixation,(ORIF), to maintain the soft tissue envelope and minimise bone healing complications. These anatomically contoured locking plates may also function as "internal external fixators", as deforming forces are resisted without excessive bony contact, preventing the compromise of periosteal blood supply.

The more established entries in the promising field of locking plate devices, the Less Invasive Stabilisation System (LISS-DepuySynthes) and the Polyaxial plate (POLYAX ®-Biomet), both offer significant theoretical advantages for the treatment of supracondylar femoral fractures associated with a total knee arthroplasty. These devices also can be inserted with relative ease by using minimally invasive techniques, provide a fixed angle construct, and improve fixation in osteoporotic bone(94). They are extramedullary, internal fixation systems that have been developed to incorporate the modern advances in this field, such as, extramedullary force carrying capacity, indirect fracture reduction, minimal implant-bone contact, in order to limit soft tissue disruption and preserve the periosteal blood supply.

1.8 Investigational (Implanted) devices

1.8.0 Less Invasive Stabilisation System (LISS)

The LISS plate is manufactured by DepuySynthes with a European headquarters in Switzerland (Luzernstrasse 21, 4528 Zuchwil, Switzerland. Tel; +41 32704060. www.depuysynthes.com). It was originally designed for the distal femur and proximal tibia. The manufacturers describe its shape as conforming to the anatomical contours of the specific area of the bone. Its instrumentation is designed to forfeit the need for an extensive incision to align the plate against the bone. This device can be introduced through a small (skin) incision via the minimally invasive plate osteosynthesis (MIPO) technique. Thus, the traditional concept of internal fixation, which requires an extensile approach to the fracture zone, is presently challenged by a more biological, atraumatic approach with careful handling of the soft-tissues (95-99).

The LISS Plating System is intended for fixation of the following fractures of the distal femur:

• Extra-articular or distal diaphyseal fractures.

• Complete intra-articular fractures including those with associated coronal fractures.

• Periprosthetic fractures.

The LISS system is available as Titanium or Stainless steel implants in a variety of sizes; 5, 7, 9, 11 and 13 hole implants. It ranges from 156-316mm in length accompanied by 5mm locking screws.

System Features

- Unicortical locking screws offer angular stability for optimal purchase and reduced stress on the bone.
- Locking screws perform drilling, tapping and locking to the plate.
- Anatomic shape of the plate and locked construct makes intraoperative contouring unnecessary.
- The availability of an insertional guide allows percutaneous targeting of screws through stab incisions allowing percutaneous, submuscular insertion of the plate with minimal disruption of the cortical blood supply.

The anatomic plate design also allows for optimised screw position in the condyles to avoid intercondylar notch and patello-femoral joint and maximise bone purchase. It is recommended that a minimum of four locking screws are used to secure the plate both proximally and distally, and in osteoporotic bone consider a greater number of screws and bicortical fixation. The plate also possess five (2mm) K-wire holes, 4 distally and one proximally for intra-operative temporary plate fixation and fracture assessment (100).

FIGURE 6: LATERAL IMAGE OF THE LISS DISTAL FEMORAL PLATE

The insert highlights corresponding locking threads on the screw head and the osteosynthesis device.

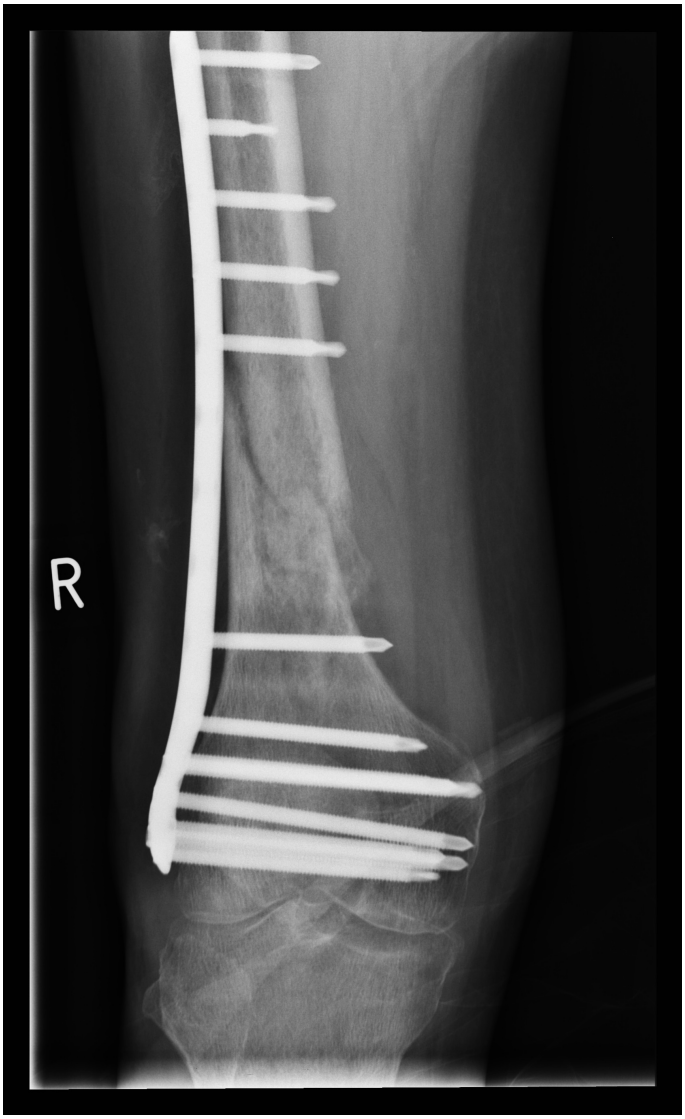


FIGURE 7: AN A-P RADIOGRAPH OF A LISS DISTAL FEMORAL FIXATION

1.8.1 POLYAX® plating system

The Polyax locked plating system is manufactured by Biomet, whose European headquarters is based in Holland (Toermalijnring 600, 3316 LC Dordrecht, The Netherlands. Tel; +31786292909. www.biometeurope.com) It is the opinion of the manufacturer that this implant is designed to give the surgeon maximum flexibility with the use of fixed-angle locking, variable-angle locking and non-locking screw options. The result is fracture fixation based on each individual patient's fracture type, bone quality and anatomy. The system is indicated for use in open or percutaneous fracture fixation cases requiring ORIF of closed and open fractures of the distal femur, including secondary augmentation of non-unions and malunions(21, 93).

The Polyax femoral plates are designed for placement on the lateral side of the distal femur and are pre-contoured to closely match the anatomy of the bones. It is intended for use in:

- Periarticular fractures
- Periprosthetic fractures
- Malunions
- Non-unions
- Osteotomies

Each plate is manufactured from TiMAX™ anodized titanium alloy Ti-6Al-4V, which gives the plates superior fatigue strength, excellent biocompatibility and optimal stress transfer. The screws are manufactured from colour-anodized titanium alloy Ti-6Al-4V for easy identification and selection in the operating room (OR). All instruments are color-coded in accordance with associated colour-anodized screws to enhance surgical efficiency. The system includes a handle and radiolucent target guide that connects to the plate for minimally invasive plate and screw insertion, as well as several tools to aid in fracture reduction.

Screw locking is accomplished either by threading a screw directly into the plate (fixed-angle construct) or into a patented polyaxial bushing (variable-angle construct) contained within the plate. The screw's locking portion consists of a triple-lead, tapered-thread on the screw head, which is designed to engage the plate or bushings. The bushings allow the surgeon to lock screws in place at a desired

angle within a maximum 30-degree cone of angulation. Non-locking screws are provided for placement in either a fixed-angle locking hole or polyaxial bushing.

Distal locking of the femoral POLYAX® locked plating system construct is accomplished by one centrally located 8.0 mm fixed-angle locking screw surrounded by four 5.5 mm polyaxial locking bushings. The proximal plate stem has threaded holes for 4.5 mm fixed angle locking or 4.5 mm non-locking screws and is anatomically contoured to match the femoral bow. Plates are available in lengths of 6, 9, 12, 15 and 18 holes (Cat. No. 8141- 30-1XX—right, Cat. No. 8141-31-1XX—left). The plate has three K-wire holes for optional intra-operative temporary fixation (101).

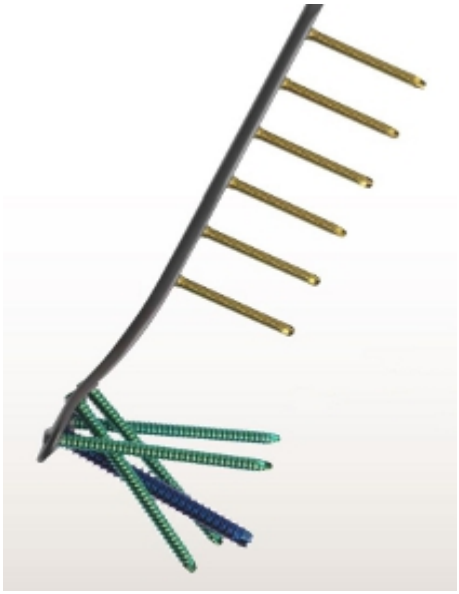


FIGURE 8: A POLYAX ® DISTAL FEMORAL PLATE

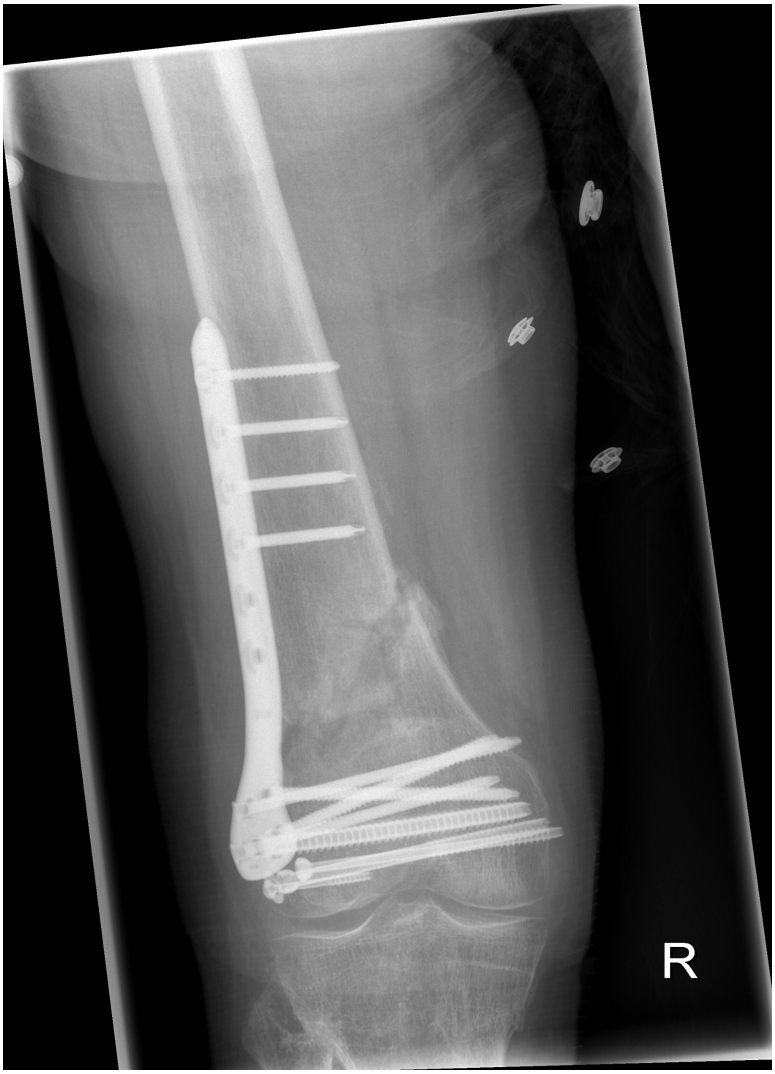


FIGURE 9: AN A-P RADIOGRAPH OF A POLYAX ® DISTAL FEMORAL FIXATION

Chapter 2

Proposed line of investigation

2.0 Investigational concept and hypothesis

A consensus on the ideal implant for the fixation of distal femoral fractures does not exist. Some surgeons favour a fixed angle locking device, whilst others prefer the flexibility of a variable angled locked device with their opinions based on familiarity or institutional affiliations.

In terms of published literature, Kregor et al (102) reported his experience of utilizing the L.I.S.S device to stabilise 13 distal femoral periprosthetic fractures above knee prostheses and reported overall complication rates of 15.4% and union rates of 84%.

A similar series by O'Toole et al (103) was published in 2006. Eleven patients with fractures occurring above knee prostheses fixed with the L.I.S.S device were studied. The authors drew favourable conclusions, as they found no complications, especially when their results were compared with those of Su et al (25), who summarized the literature on operative treatment of these fractures with an overall complication rate of 19%.

Ricci et al (104) in the same year published their prospective case series of 22 patients with 24 (2 bilateral) supracondylar femur fractures above a well-fixed non-stemmed TKA treated with the LISS plate. At an average of 15 months (range, 6-45) of follow up, 19 of 22 fractures healed after the index procedure (86%). Healing complications occurred in 16% (2 cases developed infected nonunions and 1 an aseptic nonunion). Postoperative alignment was also satisfactory in 20 of 22 patients. Hardware failures occurred in 4 cases (breakage of screws). Fifteen of 17 patients who healed returned to their baseline ambulatory status, with 5 requiring additional ambulatory support compared with baseline.

The latest evolution of locking osteosynthesis technology, which allows a variable degree of freedom of insertion of the locking screws, in a 30 degree cone of angulation, is the Polyax® plating system. The question is whether the innovative locking options, of this implant is of added value and possesses other benefits for the

stabilisation of osteoporotic fractures and periprosthetic fractures, about the knee joint, is yet to be determined.

Otto et al. and Wilkens et al published biomechanical analysis of the comparison of variable and fixed angle locking plating systems (Polyaxial vs. uniaxial locking) on synthetic femoral fractures in the Journal of Orthopaedic Trauma (105, 106). Both studies reached different conclusions. Wilkins et al favoured the polyaxial construct with greater load to failure and greater stiffness. The analysed implants in that study were manufactured by Zimmer. On the contrary, the study by Otto et al, favoured the LISS over POLYAX®. The POLYAX® system was reported to have a decreased load to failure, a lower stiffness and a lower peak force compared to the fixed angled, LISS locking system(105, 106).

The exact reasons for the Polyaxial plating system supporting less load under axial loading is unknown. It was postulated that the bushings contained within the Polyaxial plate, which allows the variable angling of the metaphyseal screws, to which the screw locks into, and not directly onto the osteosynthesis plate, as is the case with the monoaxial, fixed angled, LISS plate, might be responsible for this reduced load bearing capacity.

From a theoretical point of view, having the possibility to insert locking screws in a variable arc of 30 degrees around the metaphysis, gives the surgeon the ability to target areas of good bone stock or areas outside the zone of fracture comminution or to negotiate around pre-existing implants, all of which if not considered, may lead to a compromise of the fixation and subsequent fixation failure or loss of fracture reduction, due to inadequate purchase outside the zone of injury. Whilst this versatility of the Polyaxial plating system, is considered advantageous compared to the traditional, monoaxial (LISS) locking plating system, the existing clinical evidence to support this view remains poor. In summary, further investigation and scientific backing, in the form of a clinical trial, is desirable to evaluate the theoretical advantage of the newer, multiaxial locking of the screws to the distal femoral metaphysis.

Therefore, the purpose of this study is to investigate the performance of the currently available polyaxial plating technology for the stabilisation of distal femoral fractures, particularly, in a cohort of elderly patients with osteoporotic and periprosthetic fractures.

The author hypothesizes that the use of the POLYAX® locked plating system (Biomet) is equally as effective as the fixed angle system, L.I.S.S (DepuySynthes) in the treatment of osteoporotic and periprosthetic distal femoral fractures, inferring no statistically significant difference between both plating systems. In order words, both systems will achieve similar fracture union rates at comparable time frames. This is the null hypothesis and primary outcome that will be explored by this prospective randomised trial.

2.1 Aims and objectives

This pilot study aims to provide preliminary evidence on the use of two different plating systems on the operative management of osteoporotic or periprosthetic distal femoral fractures. In addition to providing evidence allowing the acceptance or refuting of the null hypothesis. This clinical trial will also provide data for sample-size calculations, which will facilitate the set up and design of subsequent larger scale randomised, multi-centre, clinical trials of adequate sample size to identify statistical significant differences in treatment methods.

Therefore, the objective of this pilot study is to explore osteoporotic and periprosthetic distal femur fractures in a complex group of patients, requiring surgical intervention, with a mono-angled versus a poly-angled locking osteosynthesis device, in order to establish whether the type of fixation employed impacts on patients' outcome.

The null hypothesis that osteosynthesis with the polyaxial plating system of periprosthetic or osteoporotic fractures of the distal femoral metaphysis achieves similar union rates, at comparable time frames, compared with the LISS plating system.

The secondary clinical outcomes include:

1. Critical comparison of the intraoperative details of the use of the two implants (operative duration and the length of the surgical incision)
2. Comparison of the incidence of intra- and post-operative early and late complications.
3. Comparison of the incidence of hardware failure and secondary interventions

4. Comparison of the functional outcome and health related quality of life outcome, as recorded by the Oxford Knee Score(107) and EuroQol, EQ-5D(108). These evaluations will be obtained at all designated evaluation points.

2.2 Trial recruitment criteria

2.2.0 Inclusion criteria:

1. Subject is able to give informed written consent to participate in the study, by signing relevant study material, including confidentiality agreement, consent forms and patient information leaflets, as sanctioned by the Institutional Review Board/Ethics Committee.
2. Subject must require surgical treatment of a periprosthetic fracture adjacent to components of a total knee arthroplasty, or an osteoporotic distal femoral fracture.
3. Subject is skeletally mature (≥18 years of age or radiographic evidence of closure of epiphyses).
4. Subject was able to ambulate satisfactorily prior to the fracture incident.
5. Subject agrees to participate in the post-operative clinical evaluations.

2.2.1 Exclusion criteria:

1. Subject who has a clinically significant organic disease, including cardiovascular, hepatic, pulmonary, neurologic, or renal disease, or established dementia or other medical condition, serious intercurrent illness, or extenuating circumstance that, in the opinion of the Investigators, would preclude participation in the trial or potentially decrease survival or interfere with ambulation or rehabilitation.
2. Subject whose fracture is the result of an infection.
3. Subject with known metabolic bone disease or other condition (other than osteoporosis), which would negatively impact on the bone healing process (e.g. history of Paget's disease).
4. Subject currently being treated with radiation, chemotherapy immunosuppression, or chronic high-dose steroid therapy.
5. Subject has other fractures that would interfere with ambulation or rehabilitation.
6. Subject is at high risk of developing osteomyelitis (open fractures extensive/contaminated soft tissue injuries).
7. Subject has an American Society of Anaesthesiologists (ASA) Physical Status Classification greater than 3.
8. Subject has a life expectancy less than 24 months.
9. Subject whose fracture is accompanied with a loosening of the original prosthesis. This may be determined preoperatively or intraoperatively, in which case, intraoperative exclusion of the patient is necessary.

Chapter 3

Patients and Methods

3.0 Research approval

Common amongst clinical research trials is the aim of providing answers to clinical questions, which are relevant to that particular field of medicine and impacts on patient-care, directly or otherwise. Adhering to good clinical practise guidelines, patient safety should remain paramount during all clinical trials and adverse events should recorded, reported and investigated appropriately. This prospective clinical research trial, which was conducted by myself and my colleagues, was no different, adhering to these principles and the declaration of Helsinki robustly.

Both the local and regional authorities sanctioned this study. Full ethical and research approval was granted in 2009 by the Northern and Yorkshire Research Ethics Committee, room 215 TEDCO Business centre, Viking Industrial park, Rolling mill road, Jarrow, Tyne &Wear, NE32 3DT. Telephone; 01914283545/ Fax; 01914283303.

The study title: A randomised controlled Trial of different locking plate fixation systems for periprosthetic or osteoporotic distal femoral fracture: Polyaxial locking plating system (POLYAX plate, Biomet) versus Less Invasive Stabilisation System (LISS plate, DePuySynthes)- a pilot study (REC reference number: 08/H0903/26).

The study is also approved locally by the Research and Development (R&D) department of Leeds Teaching hospitals NHS Trust, Research and Innovations department, 34 Hyde Terrace, Leeds, LS2 9LN. Telephone: 01133920144. (R&D reference: OR08/8597).

The body of work detailed in this thesis, ranging from patient identification, recruitment, clinical data collection and analysis, clinical follow-up and the initiation and co-ordination of the secondary sites, was undertaken by myself, as a member of the clinical research team of the Academic Unit of Trauma and Orthopaedics, floor A, clarendon wing, Leeds General Infirmary, Great George street, Leeds, United Kingdom.

In this case, the lack of clinical evidence to support the use of polyaxial plate fixation over a fixed angle construct or vice versa (POLYAX Vs. LISS systems), lead to the null hypothesis of similar outcomes between both fixation methods. A study protocol was drawn up by my colleagues, Mr N. Kanakaris and Professor P.V. Giannoudis, after a literature review identified a lack of clinical evidence on the subject. On the back of this, a funding application was made and following the acquisition of a research grant, an application for ethical approval was initiated.

This pilot clinical research trial was funded by Depuy Synthes UK, capitol Boulevard unit 1, Capitol park, Leeds, LS27 0TS.

After the revised version of the protocol was submitted, a favourable opinion was given by the Northern and Yorkshire Research Ethics Committee on the 29/08/2008. This allowed a sponsorship application to the University of Leeds, Faculty of Medicine and Health, Level 10, Room 10.110, Worsley Building, Leeds, LS29NL. Telephone: 01133434974, to be made. Again a favourable outcome followed the sponsorship application.

Lastly a similar application and a business case was put forward to the R&D department of Leeds Teaching Hospitals NHS Trust and Musculoskeletal department of Leeds General Infirmary. Local and departmental approval was obtained before the trial initiation commenced.

During the course of this trial, the author submitted amendments of the study protocol, in addition to annual progress reports to the Northern and Yorkshire Research Ethics Committee (NYREC). These amendments received a favourable opinion from the committee.

3.1 Protocol Amendments

Three amendments to the initial study protocol were made by the author, after the study commenced. The first was an amendment of the number of participants. Our initial postulate was for 60 patients, 30 in each arm of the trial (30 patients randomised to the POLYAX group and 30 patients randomised to the LISS group). This figure was revised after we fell short of our recruitment target for the first 12 months. The reasons for this will be discussed in more detail in subsequent chapters. The issues we faced included a seasonal variation in the frequency of admissions with distal femoral fractures and the majority of the cases admitted with appropriate injuries, did not meet the eligibility criteria.

The second amendment of the protocol was made for pragmatic and monetary reasons. The randomisation process was amended due to financial constraints. Initially, the randomisation was planned to be undertaking centrally contracting the Clinical Trials Research Unit's (CTRU), part of the Leeds Institute of Molecular Medicine, Faculty of Medicine and Health, at the University of Leeds. The CTRU works closely with both local and national institutions, providing research support including an automated 24-hour telephone randomisation system. This amendment allowed for a more simplistic and economically viable randomisation process. This was a ballot style system of randomisation of the recruited patients into either arm of the trial. The responsibility for this process was another of my duties.

The third amendment to the protocol was made after a monitoring visit by a representative of the study sponsor, the University of Leeds. This amendment involved our radiological analysis and reporting. The initial protocol stated all radiographs and cross-sectional imaging would be reported by a fellowship trained musculoskeletal radiologist. Due to financial and logistical constraints, the protocol was altered to allow the radiological assessments to be performed by independent fellowship trained orthopaedic and trauma surgeons, which does not diminish the strength of our study.

3.2 Study design and participating institutions

This pilot study is designed as a multicentre prospective randomised device trial. Patients will be enrolled at 4 (four) institutions. Senior Orthopaedic Surgeons will use one of two investigation devices to treat 40 patients who have sustained distal femoral osteoporotic or periprosthetic femoral fractures around a knee arthroplasty.

Patients diagnosed with a periprosthetic fractures around a total knee arthroplasty with non compromised-stable femoral component (Rorabeck type II), or those with osteoporotic fractures of the distal femur will be recruited via the medical institutions of the participating Investigators and randomised into one of the two arms of the study. Periprosthetic or osteoporotic distal femoral fractures will not be considered separately and the endpoint will be the number of 40 patients altogether.

The primary trial site, followed by the secondary sites are listed below. For each site the corresponding operating surgeon or surgeons are named within the brackets.

1. Leeds General Infirmary (N. Kanakaris / P.V. Giannoudis)
2. Bradford Royal Infirmary (D. Shaw)
3. University Hospital Coventry (M. Krkovic)
4. University Hospital of Wales (K. Mohanty)

Proposed groups:

Group A: 20 cases of distal femoral fractures (osteoporotic or periprosthetic) treated operatively with a POLYAX® locked plating system

Group B: 20 cases of distal femoral fractures (osteoporotic or periprosthetic) treated operatively with a LISS locked plating system.

All the patients will be assessed on recruitment and at 1 month, 3 months, 6 months, 9 months and 12 months post-operatively, unless further or more frequent reviews are clinically indicated. This is the standard follow-up regime for distal femoral fractures. At each trial visit, study specific data was collected as outlined in the table below (table 4).

Table 4: Data Collection scheduling

Assessment time points		Baseline	4 weeks	3months	6months	9months	12months
1	Clinical Examination	X	X	X	X	X	X
2	CCI	X					
3	EuroQol, EQ-5D	X	X	X	X	X	X
4	OKS	X	X	X	X	X	X
6	X-ray (A.P/Lateral)	X	X	X	X	X	X
7	CT scan (optional)				X		X
8	Haematology tests	X					
9	Biochemistry tests	X					

The subject will be blinded to the type of fixation they have received. The operating team will be unaware of the implanting device until the time of randomisation.

3.3 Clinical assessment tools

Two widely accepted and validated outcome measures, the Oxford knee score and the European Quality of Life tool, were used for the clinical assessment of study candidates, at each visit.

3.3.0 Oxford knee Score

The Oxford knee score was developed at the University of Oxford and Nuffield orthopaedic centre by Dawson et al in 1998. This questionnaire was born out of the need for a relatively short questionnaire, imposing very little burden on the patient, with a specific focus on knee pathologies, especially osteoarthritis. It main use is as an outcome measure following total knee replacement surgery. The OKS is a valid knee scoring tool that is reproducible, with high internal consistency and test-retest reliability (107).

It is composed of 12 subjective questions on knee function, each with a weighing score of 1 to 5, with more severe symptoms having a higher score. Pain and disability weigh more heavily. A minimum score of 12 is expected for a patient with normal function and a maximum score of 60 can be attained in patients with poor knee function.

In summary the OKS provides a validated outcome measure for TKR that is short, practical, reliable and sensitive to clinically important changes over time and it is one of the 3 most commonly used knee scoring systems used in the United Kingdom (107, 109). Although this scoring system was developed the assessment of knee osteoarthiritis and its related interventions, it is also very apt for the assessment of traumatic conditions around the knee joint, as the symptoms and functional impairment suffered by afflicted patients, in both groups, are essentially homogenous.

3.3.1 EuroQOL (EQ-5D)

EQ-5D is a standardised measure of health status developed by the EuroQol group in order to provide a simple, generic measure of health for clinical and economic appraisal (110).

The EuroQol group is a network of international multidisciplinary researchers, set up in 1987, devoted to the measurement of health status, from all over the world. The EQ-5D tool is applicable to a wide range of conditions and interventions, and it provides a descriptive profile and a single index value for health status that can be used for the clinical and economic evaluation of health care, in addition to population health surveys.

EQ-5D is cognitively unchallenging and its design allows self-completion by participants within minutes of commencing. This tool is ideal for postal surveys, for face-to-face interviews and in a clinic setting. It is widely accepted and extensively employed for clinical trials, observational studies and other health surveys purposes.

The EQ-5D is essentially composed of 2 broad categories; the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS). The EQ-5D descriptive system comprises of 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension or element has 3 levels; 1 (no problem), 2 (some problems) and 3(extreme problems). The respondent is asked to indicate his or her health state by either ticking, circling or placing a cross in the box against the most appropriate statement in each of the 5 dimensions.

Lastly, the respondent indicates their self-rated health on a vertical, visual analogue scale, with endpoints labelled “Best imaginable health state” and “Worst imaginable health state” on either end of the scale spectrum. This information can be used as a quantitative measure of health outcome as judge by the individuals responses, compared with the reference values for the given population to which they belong.

3.3.2 Charlson Comorbidity Index (CCI)

CCI is a validated tool for classifying comorbid conditions which may alter the risk of mortality within a studied population. Developed in 1987, based on a cohort of internal medicine patients admitted to a single New York Hospital, the CCI was

designed for use in prospective, longitudinal studies as a predictor of mortality risk (111).

The index takes into account 19 medical conditions, weighted 1-6 with cumulative scores ranging from 0-36 depending on the presence of pre-existing medical conditions. For example, a metastatic solid tumour and acquired immunodeficiency syndrome are both assigned a score of 6 respectively.

The one-year mortality rates for scores 0-5 are as follows: 0 (12%), 1-2 (26%), 3-4(52%), ≥ 5(85%). This translates to an increased cumulative mortality rate with each stepwise increase in comorbidity index score. The CCI is also adapted to account for increasing age. During the validation phase of that landmark study by Charlson et al, age was also found to be an independent risk factor for death from a comorbid condition. Therefore, to account for the effects of the patient's increasing age, one point should be added to the CCI score for each decade of life over the age of 50 years (111).

3.4 Duration of study

A study period of four years was initially proposed and recruitment was expected to be completed within three years, according to our forecasts, allowing a time of 12 months for clinical and radiological follow-up and data collection. All recruited patients were expected to undertake a minimum of 12 months of follow-up after their index fracture fixation procedure. A 12-month extension to the study was sought from the overseeing Research and Ethics Committee, due to slower than anticipated patient recruitment.

3.5 Patient evaluation and clinical stabilisation

All patients admitted to the 4 study institutions, with distal femoral fractures, were evaluated and screened accordingly for possible recruitment into the study.

The assessment and initial management of all patients admitted acutely, with distal femoral fractures, regardless of whether they were potential study candidates or not, was standardised and adherent to Advanced Trauma life Support (ATLS) principles. This took place in the Emergency department by the hospital's trauma team. Elderly, osteoporotic, patients admitted with distal femoral fractures usually suffer isolated injuries and although concomitant injuries may occur, this is by far the minority.

A high clinical index of suspicion for associated injuries was maintained throughout the acute management of the afflicted patients. A collateral history was sought, in relevant cases, and careful multi-system evaluation and documentation was performed in all cases.

After the initial patient management and cardio-respiratory stabilisation, appropriate analgesia was administered before fracture splinting and radiological investigations were performed. All cases had an AP and lateral radiographs of their femur, hip and knee joints before transfer to the trauma ward, where further pre-operative medical optimisation continued until the point of operative management. All patients received both pharmacological and mechanical treatment for the prevention of venous thrombosis.

3.6 Patient Screening

Screening for relevant cases took place on a daily basis and involved a high level of collaboration between the on call trauma team and the research teams. After the admission of a potential trial candidate, the research team were informed and the relevant details were recorded in the screening log. Following this, a review of the patient's images and clinical records took place and patients that met the inclusion criteria and had no reason not to be considered, where approached by the research team. These patients routinely had 24 hours to digest the information given by the research team, which was also the printed on the patient information document and was left at their disposal. They were re-visited the following day to clarify any additional questions they had before they were consented for inclusion in the study.

A copy of the consent form can be found in the appendix.

3.7 Consent process

All patients were consented for participation in this clinical trial in-line with Good Clinical Practise guidelines. Surgical consent was also obtained, in some cases, by the research team at the time of consent to participate in the trial. All surgical consents, where performed in-line with their institutions policy on surgical consent. In each case, the correct surgical site was denoted clearly with a large arrow, drawn on the injured limb with a permanent marker-pen, after clinical examination and radiological confirmation. The patients clinical trial status was also recorded in the patient's case notes, boldly on their consent form and in the individual patient's Clinical Research File (CRF).

According to research protocol, a copy of the research consent form, patient information document, document of notification of recruitment into the research trial and a General Practitioner notification letter, were filed in the patient's case notes. The original copy of the research consent form was filed in the Trial Master file (TMF) and a copy of the surgical consent, was given to the patient.

3.8 Randomisation and Blinding

As mentioned previously, all study patients were randomised into either the Polyax group or the control, LISS group via a ballot system. This was performed centrally, at the trial primary site, Leeds General Infirmary, by the author. The operating surgeon was blinded to which arm of the study (Polyaxial or LISS plating system) the patient would belong to, until the day of surgery. The patient was also blinded, unaware of which device was implanted throughout the study period.

3.9 Radiographic evaluation

AP and lateral radiographs of the femur and the knee will be taken at all indicated time points. Two fellowship trained trauma and orthopaedic surgeons will review the images, in order to determine radiographic outcome, e.g. union/nonunion and alignment. A third independent surgeon, blinded to the two previous assessments, will evaluate and determine the outcome of the radiographs, lacking a unanimous outcome from the two previous reviews.

In cases where the plain radiographs prove to be inconclusive, detailed cross-sectional imaging is indicated. This would usually occur after 6 post-operative months or whenever it is clinically indicated. This is also the standard method of assessing fracture healing whenever a definite diagnosis cannot be made by plain radiographs.

For the purpose of this study and in-line with current orthopaedic practices, we conducted this clinical trial with the following outcome definitions;

Union: Disappearance of fracture lines or the appearance of bridging callus on at least 3 cortices, on AP and lateral radiographs or on cross-sectional imaging.

Delayed union: A lack of bony union or bridging callus across the fracture sites on plain radiographs or cross-sectional imaging, after a 6-month period.

Nonunion: Failure of the fracture line to completely obliterate on the AP and lateral radiograph or on cross-sectional imaging by 9 post-operative months.

Malunion: Shortening >2 cm, Varus or Valgus >10°, Rotational deformity >15°.

Hardware Failure: plate or screw breakage or displacement.

Osteoporosis: Singh index – grade<4 as determined via an AP radiograph of the proximal femur (112).

3.9.0 The diagnosis & grading of osteoporosis; clinical use of Singh's Index

The diagnosis of osteoporosis according to the WHO definition of the disease, requires the measurement of the patient's bone density and the use of a DEXA scanner. Bone density scanning is not routinely performed in an acute trauma management setting. Fortunately a bone density scan is readily available to all patients suspected of suffering from osteoporosis or those with fragility fractures in the U.K. But this is not the case in other parts of the world, especially in developing countries, were resources are limited.

Singh et al proposed an easy way to diagnose osteoporosis in patients with femoral fractures, which negates the need for additional imaging, a method we have employed for this cohort of patients. The cancellous bone of the upper end of the femur is composed of trabecular bone, which forms two main intersecting arches as a result of the forces acting on the proximal femur. These trabecular patterns are arranged along the lines of compression and tension stresses produced during weight-bearing and locomotion (6).

Singh et al postulated that changes in the bone architecture due to osteoporosis will have an effect on these trabecular patterns . His research conducted in Rohtak, India, at the Medical College Hospital, went on to become a pivotal paper on the subject. Now the Singh's index is widely used in research and clinical practice due to its diagnostic simplicity, as it requires only a plain hip radiograph. According to this landmark publication, osteoporosis can be diagnosed and graded from the presence or absence of trabecular lines in the proximal femur on plain radiograph (112).

The normal trabecular architectural patterns in the proximal femur include the principle compressive group, which extends from the medial cortex of the shaft to the upper portion of the head of the femur, in slightly curved radial lines. The

secondary compressive group arise below the principal compressive group, from the medial cortex of the shaft and curve upwards and laterally towards the greater trochanter. The principle tensile group arise from the lateral cortex below the greater trochanter and curve upwards and medially to the inferior portion of the femoral head. The next group of trabecular lines, the secondary tensile group, arise from the lateral cortex below the primary tensile trabeculae. This group arches upward and medially across the upper end of the femur. Lastly, the greater trochanter group, these are slender few and poorly defined tensile trabeculae that arise form the lateral cortex just below the greater trochanter, sweeping superiorly (5, 6).

Singh et al reviewed the radiographs and iliac crest bone biopsies of 35 patients recruited for their study. The histological specimens were prepared and graded following the Beck & Nordin grading of osteoporosis (113). Singh et al concluded that observed progressive changes occurred in the trabeculae of the upper end of the femur as normal bone deteriorates to osteoporosis. Six different trabeculae patterns can be recognised with increasing severity of bone loss. They concluded that simple radiographs can be used to diagnose and grade osteoporosis satisfactorily (Figure 10),(112).

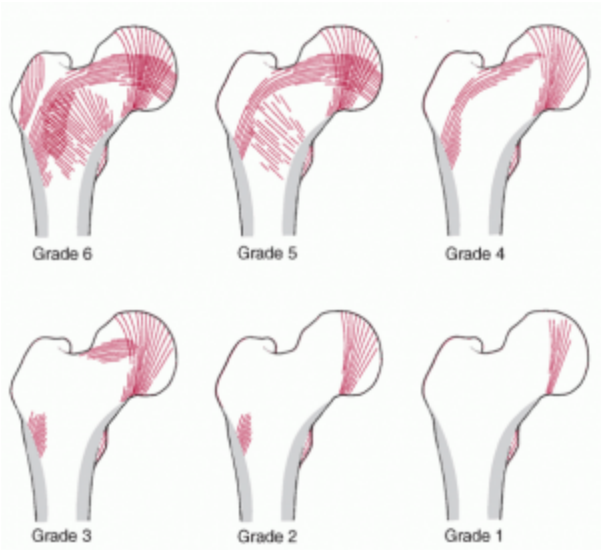


FIGURE 10: SINGH INDEX GRADING FOR OSTEOPOROSIS BASED ON RADIOGRAPHIC TRABECULAR PATTERNS OF THE PROXIMAL FEMUR

3.10 Clinical and laboratory evaluations

On admission, the following clinical laboratory evaluations were performed. These tests are standard pre-operative evaluation tests for all trauma admissions:

Haematology: Full Blood Count; white blood cell, count, red blood cell count, haemoglobin, haematocrit and platelet count.

Biochemistry: Sodium, potassium, urea and creatinine. If clinically indicated, C-reactive protein levels were also assessed.

Clotting Screening: An international normalised ratio (INR) was also checked as parting of the clotting screen. An INR of < 1.5 had to be recorded before operative intervention was considered, to minimise the risk of severe intra-operative haemorrhage.

Clinical laboratory evaluations were performed using laboratory equipment. Results outside the normal reference ranges, which were clinically relevant, were investigated and managed accordingly.

3.11 Surgery

On the day of surgery all patients were prepared for theatre according to their institutions pre-operative checklist before departing from the trauma ward. The operating team in each institution consisted of a fellowship trained Trauma and Orthopaedic surgeon, a fellowship trained anaesthetist, a surgical assistant, a surgical scrub nurse, a radiographer and other operating department practitioners. Before the arrival of the patient to the anaesthetic room, an operating team briefing was undertaking to introduce members, designate roles, discuss the operative steps and special equipment requirements or concerns, which would have been highlighted during the pre-operative planning and templating meeting.

It is standard that all patients have their last low molecular-weight heparin (LMWH) subcutaneous injection at least 12 hours prior to surgery. Prophylactic antibiotics were also administered at anaesthetic induction in all cases, according to local microbiology protocols. Most institutions favoured 400mg of Teicoplanin and 1-1.5mg/kg of gentamycin intravenously, due to the high risk of clostridium difficle diarrhoea, with cephalosporin use in elderly patients.

WHO surgical safety checklist was performed in all cases after the transfer of the anaesthetised patient onto the operating table, before the operation commenced. The checklist was completed at the end of the procedure before the patient is transferred out of the operating theatre. This process maximises patient safety by minimising the risk of intra-operative errors.

All operative procedures were performed in well equipped laminar flow orthopaedic operating theatres, stocked with the appropriate implants, under sterile conditions with image guidance, in-line with standard orthopaedic trauma operating principles for the fixation of distal femoral fractures, some of which are summarised below:

-Supine patient position on a radiolucent table with or without a sandbag underneath the buttock of the injured limb.

- Image intensifier positioned entering the operative field from the opposite side to offer maximal radiographic images with minimal surgical interference.

- The injured limb prepared with an appropriate antiseptic solution and draped allowing sterile access to the operative field (the proximal tibia to the greater trochanter of the femur).

- A sterile bolster is positioned underneath the ipsilateral knee, acting as a fracture reduction aid by allowing a varying degree of hip and knee flexion, during reduction manoeuvres. It also serves to isolate the injured limb during intra-operative lateral fluoroscopic assessments, (Figure 11).

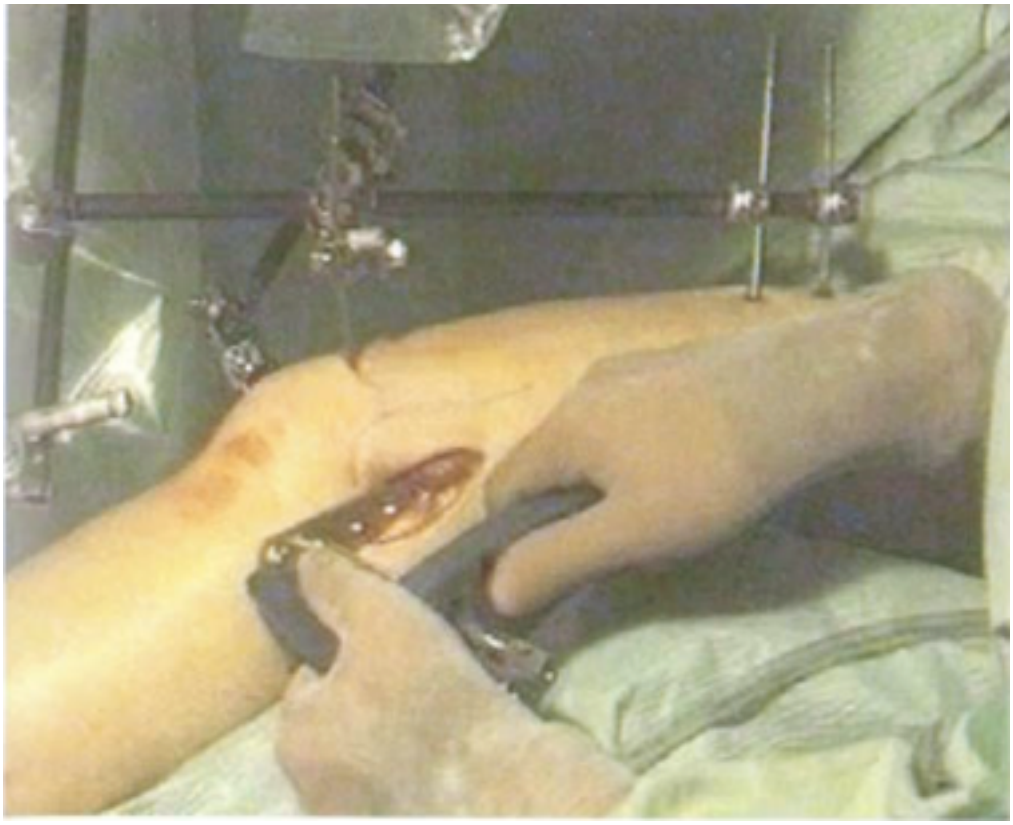


FIGURE 11: INSERTION OF A LISS PLATE IN THE FIXATION OF A DISTAL FEMORAL FRACTURE WITH THE LIMB POSITIONED ON A STERILE BOLSTER*

* IMAGES COPIED WITH PERMISSION (114).

- A lateral approach was the incision of choice. The incision was centred over the middle of the distal femur, 2-3cm proximal to the joint line, (Figure 12).

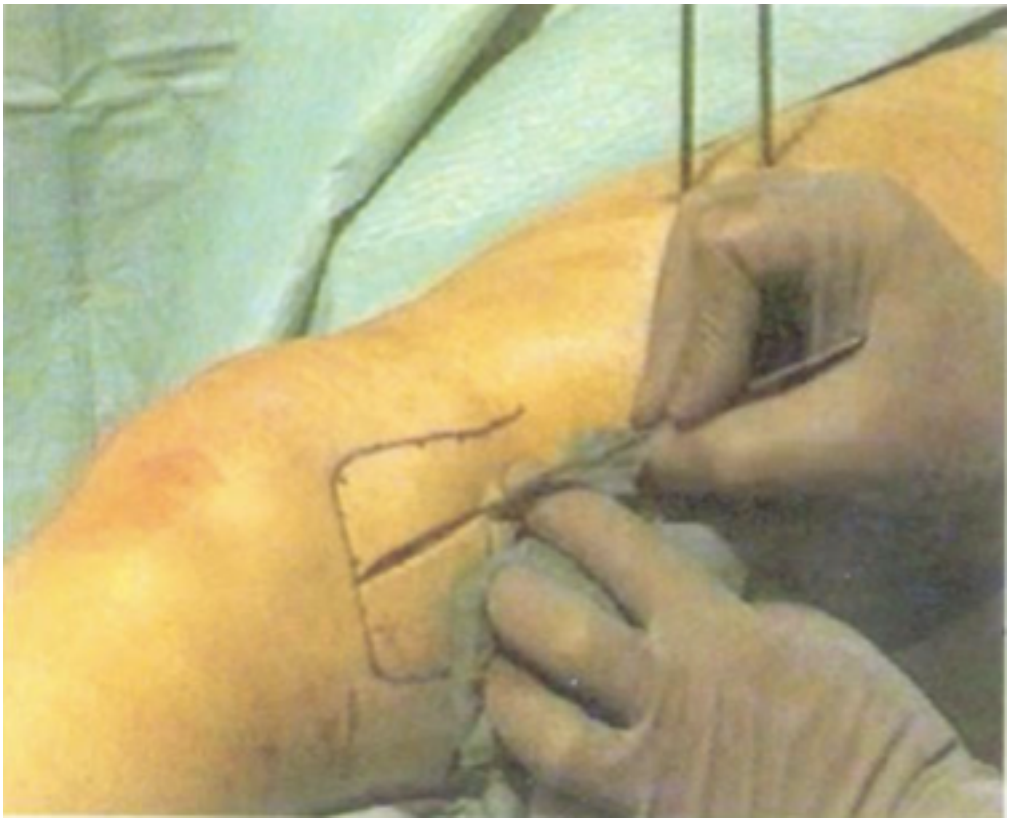


FIGURE 12: SURGICAL (LATERAL) APPROACH TO THE DISTAL FEMUR *

* IMAGES COPIED WITH PERMISSION (114).

- Minimally invasive percutaneous plate osteosynthesis (MIPPO) was attempted in all cases. The technical demands of the more complex fracture pattern injuries meant a more extensile procedure, open reduction of the fracture site, was performed in selected cases.

- After the completion of fracture fixation, the surgical wound was irrigated and closed in layers with complete coverage of the implant.

3.12 Post-operative rehabilitation

All patients enrolled into the study in all four of the University teaching hospitals involved in this clinical trial had a standardised post-operative rehabilitation regime.

- All patients were immobilised in a plaster of Paris back slab or in an extension knee brace at the conclusion of surgery and prescribed appropriate thromboprophylaxis, before their transfer out of the operating room.

- On their first post-operative day, they were seen and assessed by the physiotherapy and rehabilitation team. The immobilisation device was then changed to a functional knee brace, also referred to as a hinged knee brace and initially set to 0-30 or 0-40 degrees of freedom for range of motion.

- Active assisted range of motion and isometric exercises were initiated from the first or second post-operative day.

- All Patients were initially restricted to non-weight or toe-touch weight-bearing on the affected limb for a minimum period of 4 to 8 weeks after surgery. When the exact length of restriction was reached after clinical and radiological review, which took place at 4 weeks post-surgery, patients were allowed to progress to further loading of the affected extremity(partial weight-bearing) and all patients were fully weight bearing.

- Range of movement of each patient was monitored by the physiotherapy team and the functional knee brace was gradually increased to allow a range of 0- 90 degrees of freedom by the fourth post-operative week.

- In a handful of cases, the physiotherapy team was issued with specific instructions for post-operative rehabilitation, in cases where the fracture configuration and intervention warranted a more cautious or aggressive rehabilitation plan.

3.13 Data collection.

In addition to the demographics of the cohort, medical history and the clinical assessment parameters listed in the investigation schedule, in the study design section, intra-operative data was also collated, these include:

- Date of surgery.
- Randomisation Information.
- Stability of the knee prosthesis and additional surgical procedures performed during the operation.
- Operation time (time from the opening incision up to wound closure).
- Total length of incisions.
- Operative Side.
- The use of lag screws.
- Method of fracture reduction (open versus closed).
- Estimated blood loss during surgery as documented on Anaesthesia Record.

Data collection and transfer was carried out in line with the Data protection act of 1998 and Good Clinical Practice guidelines. Patient anonymity and intergrity was maintained at all times during and beyond the trial period.

3.14 Adverse incident reporting

In accordance with the guidelines of Good Clinical Practise and guidelines drawn by the Research and Ethics Council, all clinical trails must have steps in place to identity and deal with adverse incidents, ensuring the safety of participants is paramount and this study adheres to these guidelines.

The author was responsible for monitoring the safety of patients who have entered the study and reporting related events to the Medicines and Healthcare

products Regulatory Agency (MHRA). Patients were also instructed also to report any potential events to the researcher and the other members of the investigation team. The author also completed, reported and filed relevant documents for all breaches of the study protocol.

The following standardised definitions were considered throughout the course of this clinical trial.

An adverse event involving a device (ADE) is defined as any undesirable clinical occurrence in a subject whether it is considered to be device-related or not.

A serious adverse event involving a device (SADE) is defined as any ADE:

1. Leading to death
2. Leading to a serious deterioration in the health of the subject that resulted in life threatening injury or illness; resulted in a permanent impairment of a body structure or function; required in-patient hospitalisation or prolongation of existing hospitalisation; or resulted in medical or surgical intervention to prevent permanent impairment to body structure or body function;
3. Leading to fetal distress, fetal death or congenital abnormality or birth defect.

Incident reporting and further information is available via the MHRA website (115).

3.15 Statistical Analysis

Calculations were performed on a personal computer utilising Microsft Excel for Mac 2011 version 14.4.8(150116). Further statistical analysis was carried out using R version 3.1.0(2014-04-10). The R foundation for statistical computing platform: x86_64-w64-mingw32/x64 and STATA® data analysis and statistical software system on a Windows 7 operating system.

Chi-squared tests, equivalent to Z-tests for proportions, by treatment modality of the accumulated data with regards to the primary outcome, fracture union, were performed. In addition, unpaired t-tests of the difference in functional and quality of life scores at fixed time intervals were also carried out to verify or refute the trial hypothesis.

To further explore the effect of other factors on the rate of fracture union, a logistic regression of the data set was performed taking into account covariates including; implant type, age, sex, smoking, fracture type and CCI. Regression analysis of the Oxford knee scores and the EQ-5D tariffs at 6 months from the baseline score and tariffs, taking covariates into account were also undertaken. The assumption that outcome variables followed a normal distribution was not violated. Statistical significance was set to the P value < 0.05.

The statistical analysis for this project was supervised and the majority undertaken by Dr Robert West, Professor of Biostatistics, Faculty of Medicine and Health, University of Leeds, Leeds, U.K.

Chapter 4

4. Results

4.0. Study Cohort

From the time of the study initiation in December 2009 until recruitment phase for this clinical trial ceased in October 2013 all patents admitted with fractures of the distal femur across the 4 University Teaching Hospitals were considered for participation. In total 40 patients were recruited into the study out of the 73 patients admitted to the participating institutions with distal femoral fractures. The overall recruitment rate was 55% of which 34 (85%) of the cases were recruited at Leeds General Infirmary, the primary site of the study.

The reasons for a recruitment rate short of the initially forecasted rate of 90%, were common across all four institutions. The most prevalent reason for exclusion across the board was cognitive impairment and dementia. Eight (24%) of the 33 patients with appropriate fractures, who were not recruited, were cognitively impaired at the time of screening, hence ineligible for inclusion.

Therefore, the most common reason for an unsuccessful recruitment attempt was an inability of the research team to gain consent. Seven (21%) of the unrecruited patients were unwilling to participate in the trial process in line with the study protocol.

Another 7 adult patients had appropriate fracture patterns and were keen to participate but were excluded on the grounds that they were not osteoporotic according to Singh's index nor did they have a peri-prosthetic fractures. Their injuries occurred as a result of high-energy trauma, which typically affects the younger male population.

Other reasons for the lower than expected recruitment rate included:

- 2 cases had suspected pathological fractures of the distal femur.

- 2 cases were excluded because their fractures were open.

- 2 cases were excluded due to the lack of operative implants at the time of surgery impeding randomisation.

- 2 patients were excluded on the grounds of a limited pre-injury mobility. .

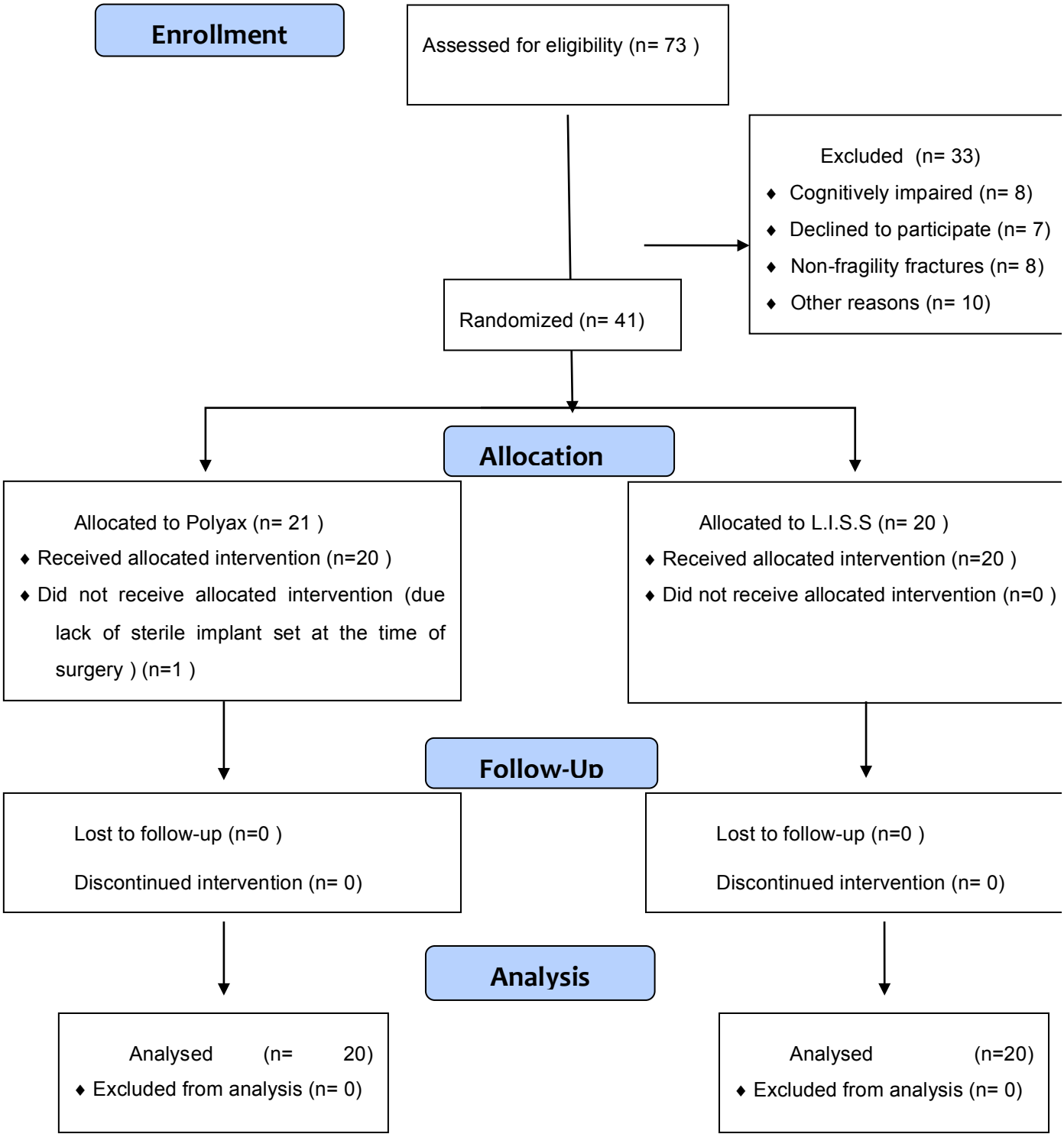
- 1 patient had a history of malignancy with a low life expectancy.

- 1 patient only spoke Punjabi, hence excluded due to the communication barrier.

- 1 patient resided in a geographical area outside the catchment area of the presenting institution.

Figure 13 is a consort flow diagram of the trial, displaying and summarising the trial activity, highlighting the number of patients screened, recruited, randomised and followed up, with the reasons for short-comings at each phase of the trial.

FIGURE 13: CONSORT FLOW DIAGRAM OF THE TRIAL PROCESS



4.1. Clinical and radiological follow-up compliance

Considering the patient compliance with the clinical and radiological follow-up schedule as outlined in the Patients and Methods chapter, it is of note that a 100% of the study cohort contributed both clinical and radiological data for statistical analysis. 25 (62.5%) of the 40 patients involved had a complete series of consecutive clinical and radiological follow up data. The remaining 15 patients (37.5%) missed one follow-up visit, due to illness, logistics or other patient related issues occurring at the time of follow-up.

A handful of patients, 3(7.5% of the cohort) did not have the full compliment of functional scoring performed at all of their follow-up visits. The main reason for this was pain. These patients were in too much discomfort for a thorough physical examination to be conducted humanely or they were too agitated to complete the relevant questionnaires appropriately.

60% of all clinical follow-up visits occurred within the designated study visit time windows or intervals, as specified in chapter 3. The remainder of the visits occurred only a few days outside the designated visit windows. The reasons for the lack of a 100% compliance, which is almost impossible in clinical studies, are consistent with the reasons for missed visits, stated above.

4.2. Demographics and Mechanism of injury

In terms of demographics, the cohort of 40 participants included 34(85%) females and 6(15%) males. The median age of the group was 77 with an age range of 55 to 99. 12 (30%) participants were above the age of 80 at the time of injury.

Mechanical falls from a standing height dominated the injury mechanism. This occurred within the home in 36 (90%) of cases. Falls outside the home were responsible for the other 4 injuries, with icy pavements implicated in 3 (75%) of those falls. 2 (33.3%) of the 6 male participants had a relatively higher-energy injury mechanism compared with the usual mechanism of falls from standing height, which dominated the female cohort. 1 (2.5%) male participant sustained his injury after a fall down a flight of stairs in his own home, secondary to alcohol intoxication. The other, a 75-year-old gamekeeper, sustained his injuries as a result of a low-speed road-traffic incident, falling off of his quad bike, whilst preparing for a hunt.

The right limb was injured in 25(62.5%) of cases whilst the left was affected in 15(37.5%) cases. All fractures were closed injuries. Open fractures were considered as an exclusion criterion, according to the trial protocol.

4.3. Fracture and osteoporosis classification

All (92.5%) but 3 patients were classified as osteoporotic according to Singh's index (<4). 1 of the 3 patients had a Singh's index of 4, according to their plain pelvic radiograph. This patient was eligible for inclusion due to her ipsilateral total knee replacement prosthesis. The other 2 patients, both of whom were clinically osteoporotic, could not be classified with the Singh index as both patients no longer possessed proximal femurs. Both patients had bilateral prosthetic proximal femurs in the form of bilateral total hip replacements in one case and bilateral hemiarthroplasties of the hip, in the other.

The fracture patterns present amongst the study cohort varied from simple extra-articular fractures to more challenging partial articular fractures. The so-called "simple fracture patterns" (33.A1 and 33.A2) were most prevalent, occurring in 31(78%) of the 40 studied patients. Peri-prosthetic fractures, above a total knee prosthesis, were also common occurring in just under half, 17 (42.5%) of the cohort. All 17 peri-prosthetic fractures were Rorabeck type II injuries, displaced fractures with a well-fixed femoral prosthesis. Table 5 displays full details of the fracture classifications and prevalence.

Table 5: The frequency and classification of the studied distal femoral fractures.

AO/OTA fracture classification	Frequency
33.A1	21
33.A2	10
33.A3	5
33.B1	1
33.B2	3
33.B3	0
33.C1	0
33.C2	0
33.C3	0

4.4. Patient factors and medications

Considering the prevalence of factors, which have an influence on bone healing amongst the study cohort, 15 (37.5%) of the 40 patients had a relevant previous medical history or drug intake.

7(17.5%) patients were known to be diabetic. Oral therapy was the prescribed treatment of choice in 5 of these patients (12.5% of the cohort). 2 patients (5% of the cohort) required insulin therapy.

Tobacco smoking, another risk factor for delayed and non-union of fractures, was only a habit practiced by 4 (10%) patients of the cohort. 1 (2.5%) other patient had a significant (60 pack/year) history of smoking tobacco, which ceased over 5 years prior to their index injury.

The chronic use of potent anti-inflammatory or disease modifying drugs, such as oral steroids or Methotrexate, was present in 4 (10%) of the cohort. At the time of injury, 2(5%) patients were receiving long-term steroid therapy and another 2 (5%) patients had Methotrexate as part of their regular medications. These patients suffered with chronic pulmonary and/ or rheumatological conditions.

In terms of the prevalence and use of antiresorptive and adjunct medications such as: Bisphosphonates, Calcium carbonate and vitamin D supplements, which are believed to have a positive impact on fracture healing, made a significant proportion of the cohort. 18 (45%) patients received either single or combined therapy during the course of the trial.

At the time of injury, 12 (30%) of the cohort were already prescribed “bone protective medication”. 7 of the 12 patients received monotherapy. This was 70mg per week of Alendronic acid orally in 3 cases, one tablet of calceos orally twice daily in 2 cases, one tablet of Adcal D3 twice daily in 1 case and one tablet of Cholecalciferol daily also in 1 case. The other 5 patients received combined therapies; 2 patients were prescribed 70mg of Alendronic acid weekly in combination with the standard calceos regime, another was prescribed the same regime but calceos was substituted by Adcal D3. 35 mg of oral Risdronate weekly in combination with Adcal D3 was prescription of choice for 1 patient. The final patient was prescribed 2grams of Strontium renelate in combination with Adcal D3.

6 (15%) of the cohort were started on antiresorptive treatment during their hospitalisation after an inpatient physician review. This is a part of the multi-disciplinary approach to the management of all patients with suspected fragility fractures. The treatment of choice was Alendronic acid in combination with calceos in 3 cases, alendronic acid in combination with Adcal D3 in 2 cases and calceos alone in 1 case. All of the above drug therapies were in line with nationally accepted guidelines.

4.5. Operative procedure and length of hospital stay

The time to surgery for this cohort of patients varied significantly. It was affected by both patient factors, such as medical optimisation prior to surgical intervention, as well as operational factors including the availability of an appropriate trauma operating list. The average time to surgery was 5.7 days (0-11).

Summarising the operative data yields the following results; 10 (25%) of cases required open reduction of the fracture site for satisfactory restoration of anatomy, prior to osteosynthesis. The median operation time was 90 minutes and the mean 101.5 minutes (60-192). The majority of patients, 75% had multiple incisions with a median incision length of 14.5cm (8-33).

Length of in-patient or hospital stay varied widely between individual patients depending on a number of factors including; the patient's general fitness and their ability to cope, their motivation to return home, home circumstance and social support networks, pre-injury mobility status, as well as, the presence of post-operative complications. The median length of hospital stay was 19 days, with a range of 4 to 43 days.

4.6. Morbidity

The overall rate of complications within this group of patients was expectedly high. As described in the demographics section, the study population consisted of predominantly an elderly cohort of patients with significant medical co-morbidities, all of whom were afflicted with a potentially life changing limb injury.

Within the defined follow-up period of 12 months, several hospitalisations of the study patients occurred for a variety of reasons, some related and others

unrelated to their index orthopaedic injury and procedure. In total, 13 hospital admissions occurred in 12 patients. The majority, 8(62%) of these admissions were secondary to respiratory compromise. The other 5 admissions occurred under the care of the orthopaedic team and will be discussed accordingly.

Medical admissions during the 12-month follow-up period included;

- 1 re-admission (patient 2) 6 days after discharge with lower respiratory tract infection.

- 3 admissions in 2 patients (patient 8 & 27), within 3 months of surgery for acute infective exacerbations of chronic obstructive pulmonary disease.

- 1 admission (patient 17) for a lower respiratory tract infection and ipsilateral calf swelling 13 weeks post-operatively. This patient developed clostridium difficile diarrhoea after 3 days of hospitalisation and treatment with intravenous antibiotics.

- 1 admission (patient 26) at 5 post-operative months, with a lower respiratory tract infection and symptoms of a cerebrovascular accident (transient ischaemic attack)

- 1 admission (patient 30) with symptoms of a lower respiratory tract infection and diarrhoea at 7.5 post-operative months. Stool cultures confirmed clostridium difficle diarrhoea.

- 1 admission (patient 22) at 9 post-operative months for the management of acute exacerbation of chronic obstructive pulmonary disease.

Five musculo-skeletal admissions during the 12-month follow-up period included;

- 1 admission with septicaemia (patient 10) at 29 post-operative days, requiring incision and drainage of a deep surgical site collection.

- 1 admission (patient 4) for revision of distal femoral fixation to a supracondylar intramedullary device after the trial implant failed (plate breakage) at 30 post-operative days with no history of trauma.

- 1 admission (patient 8) with ipsilateral displaced fractures of the proximal tibia and fibula, 5 months after the index distal femoral fixation after another mechanical fall.

- 1 admission (patient 36) for revision of distal femoral fixation to a supracondylar intramedullary device at 5 post-operative months after the investigating implant failed (distal screw cut out and breakage). The backing out of the distal fixation screws was first noticed at 3 post-operative months but an unsuccessful trial of conservative management was initially attempted, instead of extensive revision surgery, due to the patient's high anaesthetic and mortality risk.

- 1 admission (patient 16) at 6.25 post-operative months for biological augmentation of the fracture site with bone morphogenic proteins (BMP) and bone grafting due to a radiological lack of union activity on cross-sectional imaging.

The fixation implant revised in Patient 4, due to failure at 30 post-operative days, was sent back to the manufacturer for stress analysis. They reported, "fatigue failure" as the mode of implant failure.

Two further patients received musculo-skeletal reviews, in the Emergency Department of one of the participating institutions, without in-patient admission, after suffering mechanical falls at home.

- 1 patient (patient 34) sustained a dislocated shoulder joint, 10 weeks after the index procedure, which was relocated under sedation.

The other (patient 22) was diagnosed with an ipsilateral lower limb soft tissue contusion after plain radiographs of the femur and tibia did not reveal a fracture.

Both patients had trauma clinic follow up. Complete symptom resolution was the outcome for both patients after a course of physiotherapy and analgesics.

In terms of direct surgical post-operative complications, Table 6 summarises all of the post-operative complications that occurred in individual patients amongst the study cohort.

Table 6: Post-operative complications, interventions and outcomes of the trial cohort.

Post-operative complication	Time of onset (post-operative)	Treatment	Outcome
Myocardial infarction	1 day	Cardiac support at a specialist centre	Recovered
Common peroneal nerve palsy	1 day	Non-surgical (splinting)	Recovered (9 months)
Lower respiratory tract infection	4 days	I.V Antibiotics	Recovered
Pulmonary Embolus	5 days	Oxygen therapy Anticoagulation	Recovered
Deep surgical site infection	29 days	I.V Antibiotics Incision and Drainage of collection	Death
Implant failure	30 days	Revision surgery	Healed (14 months)
Deep vein thrombosis (ipsilateral)	12 weeks	Anticoagulation	Recovered
Deep vein thrombosis	12 weeks	Anticoagulation	Recovered
Implant failure	13 weeks	Revision surgery	Death

All of the direct post-operative complications and medical illness encountered by the cohort of patients within the trial period were managed in line with local institutional guidelines and protocols.

4.7. Mortality

The median CCI (charlson comorbidity index) of the entire group is 5 with a range of 2 to 9, indicating a significant 1-year mortality risk is to be expected. The actual overall mortality rate was 12.5%, 5 of the 40 patients recruited for the study, died within the 12 month follow-up period. This sub-group was comprised of 4 (80%) females and 1 male, with a mean age of 77.8 (66-99 years).

It is also worth noting that of the 5 patients that died out of the 40 participants, 3 (60%) suffered with chronic obstructive pulmonary diseases. 2 (40%) suffered from Diabetes Mellitus and 1 (20%) was on long-term steroid therapy for COPD.

Table 7 summarises the demographics and causes of death within the cohort

Table 7: Overall mortality within the cohort, the time and cause of death.

Patient	Sex	Age	Time of death (post-operative)	Cause of Death
10	Female	73	29 days	Septicaemia secondary to surgical site infection
27	Male	78	9 weeks	LRTI COPD
2	Female	99	5 months	Old age
8	Female	73	6 months	Respiratory failure LRTI
36	Female	66	7.5 months	Sepsis End-stage renal failure

4 of the 5 deaths (Patient 8, 10, 27 & 36) occurred within a hospital setting, whilst the patients were receiving active medical treatment.

Patient 36 was re-admitted with hypotension after a recent, within 2 weeks, discharge from hospital following a revision of her failed distal femoral fixation to a supracondylar intramedullary nail. This patient was known to be a high surgical risk patient as she suffered with diabetes mellitus in addition to renal failure, for which she had peritoneal dialysis. Non-operative management was initially attempted, but the decision was reversed as she suffered with severe pain, around her fractured femur, which showed no signs of healing.

Patient 2, was found unresponsive in bed by carers in her resident nursing home, after she had been put to bed uneventfully the night before.

4.8. Femoral union rates

In this cohort of patients, the rate of femoral fracture union was expectedly significantly less than 100% as 5(12.5%) of the 40 participating patients died within the 12 month follow-up period, as outlined above. At their time of death, none of the 5 affected patients were clinically or radiologically united.

Fracture union defined as, bridging callus of at least 3 out of 4 cortices on an A-P and lateral plain radiograph, was assessed at fixed time intervals and the results are outlined in Table 8.

Table 8: Overall rates of femoral fracture union at follow-up intervals.

Time	1 month	3 months	6 months	9 months	12 months
Union rate	0%	32.5%	72.5%	77.5%	77.5%

The majority (72.5%) of patients, who healed without intervention, united at 6 post-operative months. Only 2 (5%) patients healed after the six-month interval without surgical intervention.

3 other patients did not unite as expected and were labelled as having established non-union of their distal femoral fractures after appropriate surveillance and imaging, including cross-sectional scans.

Patient 16 as previously described was admitted for a secondary procedure of bone grafting using Reamer-irrigator-Aspirator (RIA) harvesting technique + BMP-7, for biological stimulation of healing, following a radiological diagnosis of delayed-union after 6 post-operative months.

Patient 5 and 6 had a longer period of surveillance, as their plain radiographs initially showed signs of healing activity but ultimately, both patients did not progress to fracture union. Subsequent secondary procedures to address their established non-unions took place at 12 post-operative months. The procedure was consistent with that carried out for patient 16, RIA bone graft + BMP-7 augmentation of the fracture site. Eventual fracture union occurred at 22 and 26 months, after their index procedures respectively.

After the exclusion of the 5 patients that died and the singular patient who underwent early revision surgery, for implant failure, 3 patients, as detailed above, underwent secondary procedures for fracture non-union. Therefore, the non-union rate within the remainder of the cohort was 8.8% (3 out of 34 cases)

Polyaxial cohort

The polyaxial arm of the study was made up of 20 patients, as is expected for a 1:1 distribution ratio. 17(85%) of the cohort were female with a median age of 73.5 years (59-99). Consistent with the entire study population, mechanical falls from a standing height again dominated the mechanism of injury and was responsible for 95% of the injuries in this sub-group.

The prevalence of Tobacco smoking, Diabetes Mellitus and the use of oral steroids and disease-modifying drugs within this sub-group was low. Only 2 (10%) patients

regularly smoked cigarettes. 3 patients (15%) were diabetic and 2 patients (10%) received regular steroid or disease-modifying drug therapy. The median CCI of the group was 5(2-8).

Simple fracture patterns (33A1/33A2) according to the AO/OTA classification system, dominated the injury patterns occurring in 14(70%) of the sub-group. 33A3 and 33B2 were the next most common fracture patterns, each occurring in 3 patients. 10(50%) of the patients treated with the Polyax system had periprosthetic fractures about a total knee replacement. All of these fractures were displaced with a well-fixed total knee prosthesis (Rorabeck II classification). Osteoporosis was also prevalent in all of these patients. The median Singh's index of the group was 2 (1-3). 4 (20%) of the 20 patients in the sub-group required intra-operative open reduction of the fracture site during their index procedures.

LISS Cohort

The LISS arm of the study was also made up of 20 patients, with 17 (85%) of the cohort being female and 3 males, a similar gender ratio to the Polyaxial group. The median age of 77 years (58-92). Consistent with the entire study population, mechanical falls from a standing height again dominated the mechanism of injury and was responsible for 95% of the injuries in this sub-group.

The prevalence of Tobacco smoking, Diabetes Mellitus and the use of oral steroids and disease-modifying drugs within the LISS sub-group was also low. Only 2(10%) patients regularly smoked cigarettes, again consistent with the Polyaxial group. 4 patients (20%) were diabetic and 3 patients (15%) received regular steroid or disease-modifying drug therapy. The median CCI of the group was 5 (2-9).

In terms of fracture classification, the simple fracture patterns (33A1/33A2), dominated the injury patterns occurring in 18 (90%) of the sub-group. The more complex, 33A3/B2 fractures occurred in 2 patients (10%) within the group. 8 (40%) of the patients treated with the LISS system had periprosthetic fractures around a total knee replacement. Similar to the former sub-group, all of these peri-prosthetic fractures were displaced with a well-fixed total knee prosthesis (Rorabeck II classification).

Osteoporosis was also prevalent in all of these patients with a median Singh's index of the group was 2 (1-4).

In this cohort of patients, 6 (30%) of the 20 patients required intra-operative open reduction of the fracture site during their index procedures, which was greater than the 4 cases that had the same undertaking in the polyaxial group.

Comparison of the Polyaxial versus LISS cohorts

Table 9 summarises the cohort characteristics for both the Polyax and the LISS sub-groups, which appear evenly matched, apart from the number of patients with complex fracture patterns, which are more prevalent in the Polyax sub-group. Figure 13 and figure 14 are boxplot representations of the age and charlson comorbidity index of the cohort with implant type.

Table 9: Cohort characteristics and post-operative complications of the Polyax and LISS subgroups

	POLYAX	LISS
Cohort number	20	20
Female: Male	17:3	17:3
Median Age (range)	73 (59-99)	77 (58-92)
Mechanism of Injury	95% low-energy	95% low-energy
CCI (median)	2	2
Simple fracture pattern (33A1/A2)	14 (70%)	18 (90%)
Complex fracture pattern (33A3/B2)	6 (30%)	2 (10%)
Peri-prosthetic fractures	10 (50%)	8 (40%)
Operation time (minutes)	107.7	95.6
Implant failure	1 (5%)	1 (5%)
Secondary procedure for non-union	2 (10%)	1 (5%)
Pulmonary embolus	1 (5%)	0
Acute Myocardial infarction	0	1 (5%)
Lower respiratory tract infection	1 (5%)	0
Deep surgical site infection	1 (5%)	0
Deep vein thrombosis	1 (5%)	1 (5%)
Common peroneal nerve palsy	0	1 (5%)
Death	3 (15%)	2 (10%)

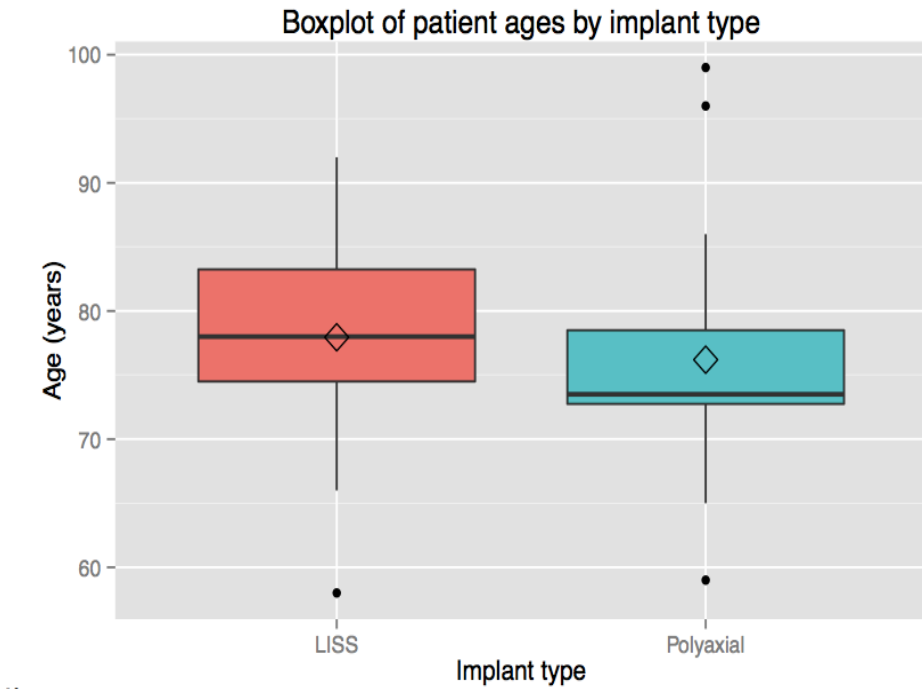


FIGURE 14: BOXPLOTS OF THE COHORT AGE BY IMPLANT TYPE

• represents the outlier data values within each cohort subgroup

◆ represents the mean value for each data set

The solid vertical line begins at the minimum value and ends at the maximum value of the dataset in a normal distribution. The 3 horizontal lines of the boxplot respresent the 25^{th} percentile, the median (thick line) and the 75^{th} percentile of each data set.

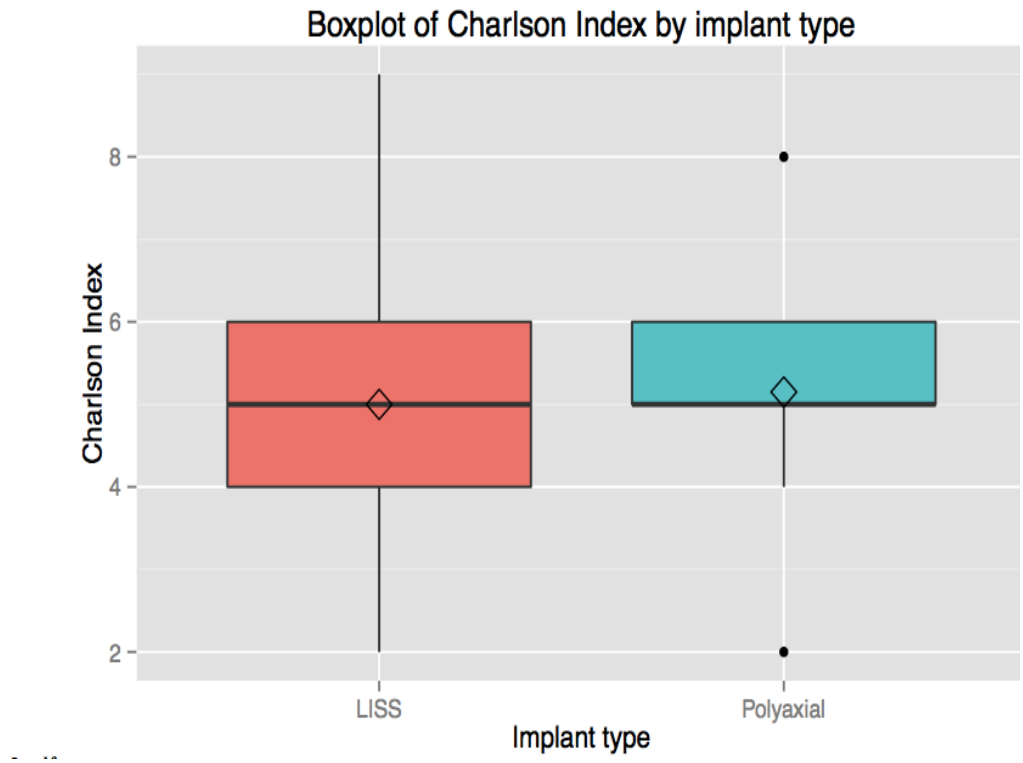


FIGURE 15: BOXPLOTS OF THE CHARLSON CO-MORBIDITY INDEX BY IMPLANT TYPE

• represents the outlier data values within each cohort subgroup

◆ represents the mean value for each data set

Again the solid vertical line begins at the minimum value and ends at the maximum value of the dataset in a normal distribution. The 3 horizontal lines of the boxplot respresent the 25th percentile, the median (thick line) and the 75th percentile of each data set.

As defined in the study protocol, a failure of fracture healing after a 6-month period was considered as delayed union. From table 8 we observe that, 94% of all the fractures, which healed without intervention, occurred by the 6-month mark. Therefore, 6 post-operative months is a valid time point to compare the variation in our primary and secondary trial outcomes with the type of fracture fixation or locking osteosynthesis implant employed.

The results of the statistical calculations to formally test our null hypothesis are as follows:

Fracture union

Within the LISS sub-group, 15 fractures were united and 3 un-united. The Polyax group contained 13 united fractures and 3 un-united fractures.

Hence estimates of the probability of non-union are:

P(Non-union given LISS) = 0.833

P(Non-union given Polyax) = 0.813

Pearson's chi-sq (1 df) = 4.8x10-31, not significant (p=0.999)

Difference in non-union rate is 0.02 and a 95% confidence limit for this difference is (-0.257, 0.299).

Oxford Knee Score

The Oxford Knee Score (OKS) was measured, after surgery for 31 patients. Regressing OKS on the type of implant (LISS or Polyax) yielded a difference in OKS of 1.51, with a 95% confidence interval of (-4.94, 7.96), p=0.643, with a lower average score for the Polyax implant.

Including the baseline measurement of OKS in the above regression greatly improved the linear model and the adjusted effect for implant was 0.79, with a 95% confidence interval of (-4.54, 6.12), p=0.769, with a higher average score for the Polyax implant.

EQ-5D tariff

There are 36 patients for whom an EQ-5D tariff was calculated at 6 months after surgery. Those patients who died were assigned an EQ-5D tariff of zero. The mean tariff for the LISS subgroup was 0.515 and for the Polyax 0.455. The difference in means was therefore 0.060 (95% CI (-0.162, 0.283). The test statistic was t=0.56, df=34, p=0.582 and thus there is little evidence of any difference in EQ-5D at 6 months.

Operation time

The 39 available operation times were compared using a Student's t-test. The test statistics is t=1.19, df=37, p=0.239. The mean operation times were 95.6 minutes for the LISS subgroup and 107.7 minutes for the Polyax cohort, so that the difference in the means is 12.1 minutes with a 95% confidence interval (-8.4, 32.5) minutes. There is little evidence for a difference in operation time.

Length of incision

The total length of incision was recorded for 36 patients, t=0.86, df=34, p=0.394. The mean lengths were 13.8 cm for the LISS and 15.4 for Polyax patients. Mean difference 1.6 (-2.3, 5.6) cm. There is little evidence of a difference in total length of incision.

Length of stay

The mean lengths of stay were 21.0 for the LISS patients and 20.3 for Polyax cohort. A difference 0.7 (-5.8, 7.2) days favouring Polyaxial, 40 patients, t=0.22, df=38, p=0.829. There is little evidence of a difference in length of stay.

Further investigation of quality of life variation over time was undertaken by the regression of EQ-5D tariff on time, implant type and covariates, taking into account the

clustering of measurements within patients by the inclusion of a random intercept term. Figure 16 depicts the evolution of EQ-5D tariffs over time following surgery.

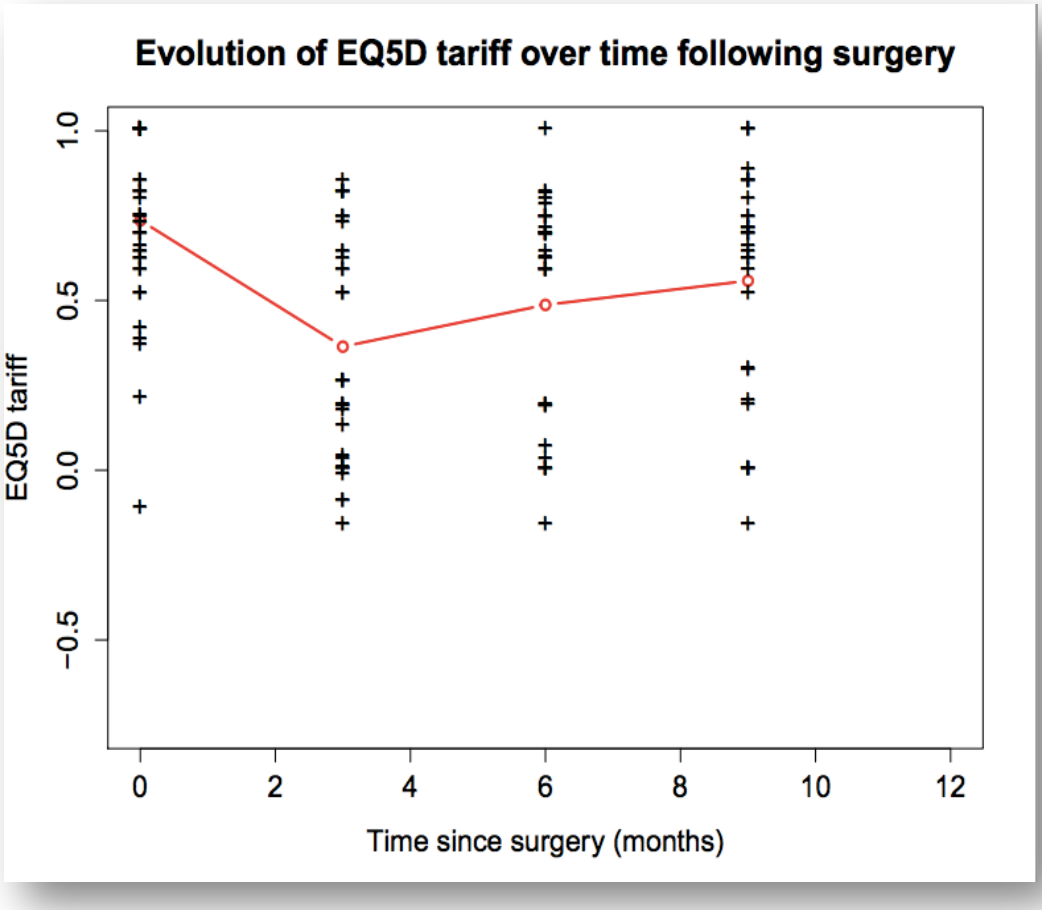


FIGURE 16: THE EVOLUTION OF THE COHORTS EQ-5D TARIFFS OVER TIME FOLLOWING SURGERY

The baseline values are plotted at the time point 0. The solid line indicates the average patient trajectory for each time point. Interpreting the trend of the average patient tariffs, it clearly shows a dip in reported quality of life measures at the 3-month mark, a time when weight bearing is still restricted and the majority of patients are radiologically ununited. The EQ-5D tariff gradually recovers towards the baseline value over the subsequent months, as more fractures unite and functional activity and independence soar. This trend may be of clinical value in the counselling of patients pre and post-operatively.

The comparison of the primary and secondary trial objectives such as; operation times, length of surgical incision and duration of hospital stay, with investigating implant type, were calculated by employing further t-tests. The results of which are contained within Table 10.

Logistic regression analysis of the EQ-5D tariffs at 6 months on the covariates; baseline EQ-5D, baseline OKS, CCI, complex fracture patterns and implant type, were also undertaken, yielding no statiscally significant association between the 6 month tariffs and the covariates, with the respective p-values; 0.70, 0.25, 0.08, 0.35 and 0.23.

Finally, a complete case regression analysis at the 6 month time point, of OKS on the baseline scores with implant type, age, sex, tobacco smoking status and CCI as covariates was also calculated. Baseline OKS was the sole covariate that showed a strong association with OKS at 6 months with a p value of $< 0.01 (t = 4.06)$.

Table 10 is a summary of the hypothesis test results for both the primary outcomes at 6 months and secondary outcomes comparing implant types (POLYAX® Vs. LISS) for the fixation of distal femur fractures.

Table 10: Summary of the statistical analysis of primary and secondary trial outcomes.

Analysis of trial outcomes by fixation device (POLYAX® Vs. LISS) ** at 6 month post intervention*	P-value	Statistical Test	Inference
Fracture union*	0.999	Pearson's chi-sq test	No statistical or clinical difference
Functional outcome (OKS) *	0.769	Regression analysis/ t-test unpaired	No statistical or clinical difference
EQ-5D tariff *	0.582	t-test unpaired	No statistical or clinical difference
Operation time	0.239	Student's t-test	No statistical or clinical difference
Length of incision	0.394	Student's t-test	No statistical or clinical difference
Duration of hospitalisation	0.829	Student's t-test	No statistical or clinical difference

Chapter 5

Discussion

5.0. Trial summary

Distal femoral fractures are a serious and potentially life-changing injury in the elderly due to the associated increased complication rates. Complications such as, infection and the need for secondary surgical procedures, to address cases of non-union or implant failure, may be increased by the presence of underlying osteoporosis and the poor physiological reserves of this group of patients. Other issues associated with individuals suffering from this injury include; a prolonged length of hospital stay and impaired ambulation. Both have a sizeable impact on the independence and the perceived quality of life of affected individuals.

In order to address the issue of fixation failures in osteoporotic bone due to screw cut-out, locked osteosynthesis fixation techniques were developed to overtake the use of non-locked osteosynthesis implants, in which the stability of the construct and the transfer of load from the bone to the implant, is dependent on the frictional force generated by the contact of the osteosynthesis plate against the underlying bone. With locked osteosynthesis devices, an angular stable, fixed-angle construct is created by the individual locking of screws onto the osteosynthesis plate.

Locked osteosynthesis devices can also be described as 'internal external fixators' as the need for a tight pressed fit against the underlying bone is unnecessary, allowing for less disruption of the periosteal blood flow, optimising the chances of fracture healing (116). Biomechanical studies using paired cadaveric femurs comparing locked with unlocked fixations have demonstrated that fixation with locked plate osteosynthesis devices are superior to conventional, unlocked implants (117, 118).

The Polyax™ plate represents a new generation of locking osteosynthesis plates, which allows 30 degrees of freedom (15 degrees in any direction), with respect to the insertion of the distal locking screws. On the other hand, the LISS implant, a first

generation locking osteosynthesis device, possesses only a mono-angle of screw insertion, which is at 90 degrees to the plane of the implant.

The theoretical advantages of the polyaxial, Polyax™ plate system cannot be disputed. It offers increased surgical flexibility, allowing the operating surgeon to bypass areas of comminution or prosthesis and target areas with adequate bone stock distally, optimising the fixation construct by a varied orientation of distal screws. Biomechanical and clinical studies have also validated the use of poly-angled locking plates for the fixation of distal femoral fractures (21, 105, 106). But the reliability of distal femoral fixations with locked polyaxial devices over mono-angled implants, has been questioned by Otto et al (105).

In that study the axial load to failure of the LISS implant was 24% greater than the load to failure of the crossed Polyax fixation and 33% greater than parallel Polyax fixation. As previously described, the 30 degrees of freedom of distal screw insertion in the polyaxial plate arises from the bushings contained within the screw holes, to which the inserted screws lock. Although this bushing technology serves as a technically advantageous development, it may also be a point of weakness, with stress concentrations at this point, leading to implant failure. Contrary, the mono-angled, LISS implant does not possess this bushing locking mechanism, as screws lock directly onto the plate. This locking mechanism, together with the higher young's modulus of stainless steel over titanium, could be the reasons for the above biomechanical observations.

A widely accepted fact, known in all fields of medicine, is the tortuous transition from laboratory advances to clinical patient benefit. Implants may yield excellent results during mechanical testing but fail in their clinical application. There is very little clinical research, in terms of publications, comparing poly-angled versus mono-angled fixations for distal femoral fractures.

Thus far, there has been one publication on the subject; "Mono- versus polyaxial locking plates in distal femur fractures: a prospective randomized multicentre clinical trial", by Hansechen et al (119). The cohort of patients recruited in that study was not restricted to osteoporotic and peri-prostheic fractures but included, relatively young

patients suffering distal femur fractures as a result of high-energy trauma. This highlights the novelty and importance of the comparative pilot trial we have undertaken.

The complication rates following distal femoral fractures vary somewhat with the patient population studied. As previously mentioned distal femoral fractures have a bimodal incidence, occurring in young individuals, as a result of high energy trauma and also predominantly in the elderly female population, as a result of low energy falls in the presence of underlying osteoporosis. These two groups vary significantly in terms of their injury patterns, physiology and co-morbidities, thus an expected difference in clinical outcome is not unreasonable.

The prospective clinical trial published by Hanschen et al, Mono- versus polyaxial locking plates in distal femoral fractures(119), reported 0% rate of surgical complications and 100% rate of fracture union in the 27 studied patients. Kregor et al published a more robust article on the treatment of distal femoral fractures using L.I.S.S implants (102). That study of 99 patients included the entire demographic spectrum of distal femoral fractures with the majority, 70%, under the age of 65 years. They reported an infection rate of 3%, a fixation failure rate of 5%, a non-union rate of 7% and a mortality rate of 5% with 1 death from a fatal pulmonary embolus.

A systematic review of 415 peri-prosthetic distal femoral fractures by Herrera et al (30), a more apt article for comparison, as the patient population studied are more aligned with our study cohort, reported an infection rate of 3%, an fixation failure rate of 4% and a non-union rate of 9%. The latter two publications are consistent with our findings of an infection rate of 2.5%, a fixation failure rate of 5%, a non-union rate of 8.8% (after the exclusion of the patients that died and underwent early revision for implant failure) and a mortality rate of 12.5%.

As previously mentioned there is just a sole publication to date exploring the clinical outcome of the management of distal femoral fractures with monoaxial versus polyaxial locking plating systems by Hanschen et al (119). This article compared outcomes for distal femoral fractures treated with the L.I.S.S system, consistent with our trial, versus the polyaxial, Non Contact Bridging system, NCB ®-DF manufactured by Zimmer. The conclusions drawn from that study are as follows; treatment with the

polyaxial, NCB® system tended to result in better functional and radiological outcomes than the L.I.S.S system.

To critique the above article by Hanschen et al, it is fair to say that their conclusions are speculative, as they are not backed by statistical analysis. The 12-month OKS for the LISS group were not available and hence not analyzed. The size of cohort was small, 27 patients (15 NCB® Vs. 12 LISS) and details such as cohort co-morbidities, complication rates, and the requirement of secondary procedures, were vaguely reported or not reported at all.

Comparing intra-operative details such as operation time and length of surgical incisions. Hanschen et al reported the mean operation time (minutes); 134.1 (LISS) versus 141.9 (NCB®). The surgical incisions were 9.6cm (LISS) versus 10.4cm (NCB®), both of which show no statistically or clinically significant difference (119). In our study, the mean operation time (minutes) and length of surgical incisions were 95.6 (LISS) versus 107.7 (Polyax®) and 13.8cm (LISS) and 15.4cm (Polyax®). Both studies show consistent reduced operation times and surgical incision length with the mono-angled, LISS devices over the poly-angled devices (NCB®/Polyax®), which are clinically and statistically insignificant.

The use of the NCB® implant instead of the Polyax® in the above study, maintains the novelty of our research trial, which compares the two leading implants (Polyax® Vs. LISS) for the fixation of distal femoral fractures in the U.K. In addition, our prospective trial involves a thorough follow-up, with the reporting of all associated events and outcomes and is backed by thorough statistical analysis.

This prospective randomised control trial has given me the opportunity not only to study the types of fixations commonly employed for the treatment of distal femoral fractures but it has also given me perspective on distal femoral fractures as a clinical entity in itself and the issues surrounding its management. In addition, it confirms the POLYAX® as a safe implant for the surgical fixation of fractures of the distal femur, achieving similar fracture union rates at comparable time frames to the mono-angled, LISS system.

One area of interest is the morbidity and mortality associated with distal femoral fractures. It is known that elderly patients with pre-existing medical conditions are the most common group of patients to be afflicted with fractures of the distal femur and that the associated morbidity of the group is high. The 12 month mortality rate of the 40 patients we studied with distal femoral fractures was 12.5%, which is just under half of the 12 month mortality rate after a neck of femur fracture; 30% -32% (3).

It is widely known that neck of femur fractures are a clinical priority in all NHS institutions, with government backed management guidelines and financial incentives, all of which have led to rise in the quality of care delivery. I believe the distal femoral fractures, although less prevalent than hip fractures, are also a challenging problem, not just for the impact it has on affected individuals and their families. Distal femoral fractures are technically more difficult to treat and take longer to unite, which leads to a delay in the return of the affected patients to normal functioning and activities of daily living, which can be detrimental to both physical and mental well being of the patient.

In terms of health economics and the cost of managing patients with distal femoral fractures versus the cost of managing patients with hip fractures, the exact figures on this matter is beyond the scope of this thesis, but it is the view of the author that both conditions are more or less equivalent, if they are considered on a case-by-case basis.

Looking at the length of hospital stay for hip fractures patients from the 2012 National Hip fracture Audit, the mean length of hospital stay is 20.2 days a drop of 5% from the previous year. This 5% reduction in the length of hospital stay resulted in reduced bed-day costs of around £14 million (3). Similarly, the average length of stay of patients with distal femoral fractures that participated in this study was 20.6 days, a figure consistent with the length of stay of hip fracture patients.

Several publications in peer review journals have associated poor outcomes with preoperative delay in hip fracture patients, two of which are cited in the 2011 NICE guidelines on hip fracture management (120, 121). The former associated a delay in operative intervention beyond 48 hours with an increased mortality risk. The latter stated that a preoperative delay does not entail adverse outcomes if the delay is for the

optimisation of comorbid medical conditions, but associated a preoperative delay beyond 48 hours, with a longer length of hospital stay.

In this prospective study, the author found no association between a preoperative delay above 48 hours and an extended length of hospital stay. 14 (35%) of the cohort has their index surgical procedure within 48 hours of admission with an average length of hospital stay of 20.4 days. 26 patients (65%) of the cohort had a preoperative delay of > 48 hours. The length of hospital stay for this subgroup was 21.5 days, which is comparatively insignificant.

With regards to the association of poor outcomes with an increased preoperative delay in hip fracture patients, we found no such association within our cohort of distal femoral fractures. The group of patients that suffered adverse outcomes (death/post-operative complications /nonunions and secondary interventions) had a marginally decreased average preoperative delay of 3.8 days compared to the 4.0 day average preoperative delay of the rest of the cohort, who suffered no complications.

Eastall et al's publication into the treatment of osteoporosis pointed out that although the burden of osteoporosis-related fractures is increasingly recognised, and although the likelihood of one fracture greatly increases the likelihood of another, orthopaedic surgeons rarely investigate or treat osteoporosis in those with such fractures (68). This trend is changing due to orthogeriatric involvement in the management of all elderly patients admitted with fragility fractures. At Leeds General Infirmary, all patients with fragility fractures who are reviewed in the outpatient fracture clinics routinely have correspondence sent out to their general practitioners highlighting their injuries as fragility fractures and requesting the initiation of appropriate treatment.

Considering the cohort of patients involved in this study, only 18 (45%) were prescribed bone protective medication at discharge after their index admission. Of these 18 patients, 12 (67%) were known to suffer with osteoporosis and where already prescribed bone protective medication at their time of injury. Therefore acute prescription of bone protective medication only took place in 6 (21%) of the 32 patients admitted with a distal femoral fragility fracture. Compare this 45% rate of discharge on bone protective medications observed in our study cohort, to the national average for neck of femur

fractures, which stands at 69%, it is clear that there is a shortfall. This shortfall highlights the need for nationally approved guidelines and protocols for the management of fractures of the distal femur.

5.1 Prevention of falls

Falls are an important cause of fragility fractures. Many attempts have been made to reduce their incidence and this continues to be an area of debate . In our study, almost all fractures resulted from a fall, most of which occurred within the home. Falling in the elderly is related to changes in gait with advancing age and the presence of other disorders, which can also affect gait and locomotion, such as Parkinson's disease, myelopathy and peripheral neuropathies (62).

The following gait changes are known to occur with advancing age; increase sway when standing, widened base, slower postural support responses , changes in the capacity to integrate sensory information and a greater reliance on proprioception, coupled with reduced speed of reflexes and reaction times, all lead to an increased likelihood of falls and fractures (62). Arthritic conditions of the lower limb resulting in joint stiffness and a decline in visual acuity due to ocular diseases, also become more prevalent with advancing age, may also be a factor for the increased incidence of falls in the elderly.

Several postulates have been made for this seasonal variation in falls and fracture incidence. Jacobsen et al 1995 concluded that factors other than weather may be linked to the seasonal variation of hip facture incidents (122). This variation was also noted in the southern hemisphere and published by Pasco et al together with proposed hypothesis to account for this trend. These include; abnormal neuromuscular function at lower temperatures, a winter–time reduction in sunlight exposure contributing to Vitamin D deficiency and proximal myopathy (123).

From the trial recruitment log of this study and similar to fractures of the hip, distal femoral fractures occur more frequently in the winter months. Over 90% of the distal femoral fractures studied occurred due to low-energy injuries, resulting from mechanical falls within the home and were not related to icy surrounds. In this age of stretched National Health Service resources, the focus on health economics and preventative health

strategies is now greater than it has ever been. The prevention of falls is paramount to the avoidance of low-energy or fragility fractures.

In more pragmatic terms, we know that osteoporosis is a risk factor for fragility fractures and that the increasing risk of falls in the elderly, for what ever reason, increases the risk of a fragility fracture, which itself is a risk factor for further fragility fractures. This vicious cycle of a fall leading to a fracture, which in turn predisposes to subsequent falls and fractures, can be halted by tackling osteoporosis and other medical conditions which affect gait and locomotion early, thus terminating the cascade.

In patients whom have already suffered a fragility fracture, the prevention or minimising the risk of further falls is imperative. These patients should receive a falls assessment and an assessment of their homes before discharge. Currently 92% of hip fracture patients receive a falls assessment before discharge (3). Speculating on the corresponding proportion of patients with fractures of the distal femur who receive such an assessment before discharge is difficult. The impression that it is significantly less, is one shared by the author.

It is the opinion of the author that distal femoral fractures and hip fractures occur in the same patient population, predominantly elderly female patients suffering from osteoporosis. These two clinical entities, are opposite ends of the spectrum of the same condition, fragility femoral fractures, as they are anatomically. Fractures of the distal femur require more formal clinical prioritisation, in the same fashion as neck of femur fractures, with accepted guidelines and management strategies, including; ortho-geriatric input during hospitalisation, timely surgical intervention, the assessment and treatment of osteoporosis and a falls assessment before discharge.

To summarise, the management of osteoporotic and periprosthetic distal femoral fractures represents a challenge for the orthopaedic and trauma surgeon. Multiple factors have to be considered during the formulation of a treatment plan, which should include pre-operative planning; a thorough consideration of fracture location and areas of comminution, the condition of the soft tissue envelope, the general fitness of the patient and their pre-injury functional capacity. In addition, the underlying bone quality, the

availability of appropriate fixation implants and the cognitive function and compliance ability of the patient, must also be considered prior to any intervention.

As previously mentioned, fractures of the distal femur predominantly affects the elderly, a group of patients who pose additional operative challenges. The invariable presence of osteoporosis is one issue. Another is the presence of pre-existing co-morbidities, which in turns affects the physiological reserves of the patient and their ability to withstand and recover from surgery, a traumatic episode in itself.

Compounding issues more common in the elderly include; an compromised soft tissue envelope (thin atrophic skin and muscles), a diseased vascular bed and an increased incidence of malnutrition, coupled with their reduced fracture healing capacity and the decreased mechanical stimuli, resulting from diminishing activity levels, all increase the risk of fracture related complications.

For the above reasons and more, the management of distal femoral fractures in the elderly must be in the form of a multi-disciplinary approach. A team approach with input from a geriatricians, surgeons, the anaesthetic team, nursing staff and allied medical specialists such as, physiotherapists and occupational therapists, is essential to address the complex needs of this group of patients, provide optimal care and a return to a level of function on par, or as close to the pre-injury functional performance as possible.

5.2 Limitations and future direction

This study has several shortcomings. The surgical fixations were performed by multiple, six, fellowship trained trauma surgeons. Their personal familiarity with either implant was not strictly ascertained prior to inclusion in the trial. Consequently, a learning curve with one or both implants at one or more of the trial centres may have occurred.

Another limitation of the study was the inability to control patient factors and adequately balance them between each treatment group. Factors such as diabetes and smoking, both negatively affect bone healing and regeneration, where not considered at the time of patient randomisation into treatment groups. The presence of pre-existing co-

morbidities which also have an impact on the patient's perceived general health and their functional capacity, and consequently affects their clinical and functional outcome scores, where also not considered at randomisation.

The randomisation process employed did not fully balance for these factors, although the demographics and characteristics of the two groups appear fairly evenly matched. The randomisation of the more complex fracture pattern injuries (33A3/ 33B2) is one area of unbalanced matching between the Polyax™ and LISS groups. The Polyax™ group contained more complex fractures, 6 versus 2 in the LISS group, and this may possibly skew the results towards the LISS device as complex fracture fixations are technically more demanding and are associated with poorer outcomes.

Above all, the most salient limitation in the interpretation of the trial results is the possibility of a type II error, due to our small sample size. This cannot also be excluded, as this trial only included 40 patients, 20 in each treatment arm.

Looking to the future and building on the work done in this pilot study, a large multi-centre collaborative international clinical trial on the surgical management of osteoporotic and periprosthetic distal femoral fractures would need to be undertaken for more robust evidence on the issue.

Post hoc sample size calculations using the STATA® data analysis and statistical software system, to ascertain the sample size required for a similar, but appropriately powered clinical trial, comparing two fixation devices.

The following assumptions, which are standard and widely accepted reference values in such clinical research calculations were applied:

- An 80% power from a test of proportions between 2 equally sized groups, diminishing the chance of a type II error to 20%.

- A detection sensitivity of at least 5% difference between the union rates of fractures treated either trial implant.

The result of the calculations and the number of patients required for an appropriately powered trial is 1890 patients, with 945 patients in each arm of the trial. Such a trial would involve a vast amount of resources and multiple centres worldwide, as

the incidence of these injuries are relatively low and a large proportion of the affected patients are cognitively impaired, hence unstable for inclusion.

Chapter 6

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Chapter 7

Appendices

7.0 Appendix 1: Ethics approvals

NHS
National Research Ethics Service

Northern & Yorkshire REC
Room 215, TEDCO Business Centre
Viking Industrial Park, Rolling Mill Road
Jarrow, Tyne & Wear
NE32 3DT

Telephone: 0191 4283545
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29 August 2008

Professor Peter V. Giannoudis
Professor of Trauma and Orthopaedic Surgery
Leeds Teaching Hospitals, School of Medicine, University of Leeds
Academic Department of Trauma and Orthopaedic
Leeds General Infirmary, Clarendon Wing, Level A
Great George street
LEEDS
LS1 3EX

Dear Professor Giannoudis

Full title of study: **A Randomised Controlled Trial of different locking plate fixation systems for Periprosthetic or Osteoporotic Distal Femoral Fractures: Polyaxial Locked Plating System (POLYAX plate, DePuy) vs. Less Invasive Stabilisation System (LISS plate, Synthes) - a pilot study.**

REC reference number: **08/H0903/26**

Thank you for your letter of 28 July 2008, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by a sub-committee.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a **favourable** ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Ethical review of research sites

The favourable opinion applies to the research sites listed on the attached form.

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission at NHS sites ("R&D approval") should be obtained from the relevant care organisation(s) in accordance with NHS research governance arrangements. Guidance on applying for NHS permission is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Notice of no objection must be obtained from the Medicines and Healthcare products Regulatory Agency (MHRA).

The sponsor is asked to provide the Committee with a copy of the notice from the MHRA, either confirming no objection or giving grounds for objection, as soon as this is available.

Approved documents

The complete list of documents reviewed and approved by the Committee (including any later versions) is as follows:

Document	*Version*	*Date*
Application	V 5.6	14 May 2008
Investigator CV	V 1 Peter V Giannoudis	08 April 2008
Investigator CV	V 1 Nikolaos K Kanakaris	08 April 2008
Protocol	Version 8.0	18 July 2008
Covering Letter	From Professor PV Giannoudis	28 March 2008
Covering Letter		28 July 2008
Letter from Sponsor	Letter from University of Leeds	14 May 2008
Peer Review	Letter from DePuy approving the study	25 February 2008
Statistician Comments	Letter from Dr RM West, University of Leeds	27 March 2008
GP/Consultant Information Sheets	Version 2.0	18 July 2008
Participant Information Sheet	Version 2.0	18 July 2008
Participant Consent Form	Version 2.0	18 July 2008
Response to Request for Further Information		
Investigatinal schedule	Version 8.0	18 July 2008
Clinical investigation plan summary	Version 8.0	18 July 2008
Evidence of Insurance MARSH	Employers,Primary Public/Products,Professional Indemnity 29/9/07-28/9/08	24 September 2007

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Now that you have completed the application process please visit the National Research Ethics Website > After Review

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

The Leeds Teaching Hospitals NHS
NHS Trust

01/06/2009

Research & Development
Leeds Teaching Hospitals NHS Trust
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Professor Peter Giannoudis
Trauma & Orthopaedic Academic Unit
Clarendon Wing
Level A
Leeds General Infirmary

Dear Professor Peter Giannoudis

Re: **LTHT R&D Approval of: A Randomised Controlled Trial of different locking plate fixation systems for Periprosthetic or Osteoporotic Distal Femoral Fractures: Polyaxial Locked Plating System (POLYAX plate, DePuy) vs. Less Invasive Stabilisation System (LISS plate, Synthes) - a pilot study.**
LTHT R&D Number: OR08/8597
MREC: 08/H0903/26
LREC: 08/H1307/77

I confirm that this study has R&D approval and the study may proceed at The Leeds Teaching Hospitals NHS Trust (LTHT). This organisational level approval is given based on the information provided in the documents listed below.

In undertaking this research you must comply with the requirements of the *Research Governance Framework for Health and Social Care* which is mandatory for all NHS employees. This document may be accessed on the R&D website http://www.leedsth.nhs.uk/sites/research_and_development/

R&D approval is given on the understanding that you comply with the requirements of the *Framework* as listed in the attached sheet "Conditions of Approval".

If you have any queries about this approval please do not hesitate to contact the R&D Department on telephone 0113 392 2878.

Indemnity Arrangements

The Leeds Teaching Hospitals NHS Trust participates in the NHS risk pooling scheme administered by the NHS Litigation Authority 'Clinical Negligence Scheme for NHS Trusts' for: (i) medical professional and/or medical malpractice liability; and (ii) general liability. NHS Indemnity for negligent harm is extended to researchers

with an employment contract (substantive or honorary) with the Trust. The Trust only accepts liability for research activity that has been managerially approved by the R&D Department.

The Trust therefore accepts liability for the above research project and extends indemnity for negligent harm to cover you as principal investigator and the researchers listed on the Site Specific Information form. Should there be any changes to the research team please ensure that you inform the R&D Department and that s/he obtains an employment contract with the Trust if required.

Yours sincerely

Dr D R Norfolk
Associate Director of R&D

Approved documents
The documents reviewed and approved are listed as follows

Document	*Version*	*Date of document*
NHS R&D Form	2.2	27/04/09
SSI Form	2.2	28/04/09
Directorate Approval		25/05/09
Radiology Approval		01/06/09
Protocol	8.0	18/07/08
REC Letter confirming favourable opinion		29/08/08
REC Letter confirming local SSA		29/08/08
Investigator Research Funding Agreement		03/12/08
Patient information sheet (MREC Approved)	2.0	18/07/08
Consent form (MREC Approved)	2.0	18/07/08
GP Letter (MREC approved)	2.0	18/07/08

7.1 Appendix 2: Protocol amendments

NHS
National Research Ethics Service

Northern and Yorkshire Research Ethics Committee

Room 002
TEDCO Business Centre
Viking Business Park
Jarrow
Tyne & Wear NE32 3DT

Telephone 0191 4283545 or 4283563 Fax 0191 4283432

Helen Wilson (Co-ordinator) e-mail: helen.wilson@suntpct.nhs.uk

08 November 2010

Mr O Obakponovew
CRF to Professor Peter V. Giannoudis
Academic Unit of Trauma and Orthopaedics
Leeds General Infirmary, Clarendon Wing, Level A
Great George Street
Leeds
LS1 3EX

Dear Mr Obakponovew

Study title:	**A Randomised Controlled Trial of different locking plate fixation systems for Periprosthetic or Osteoporotic Distal Femoral Fractures: Polyaxial Locked Plating System (POLYAX plate, DePuy) vs. Less Invasive Stabilisation System (LISS plate, Synthes) - a pilot study.**
REC reference:	**08/H0903/26**
Protocol number:	**v 7.0, 20-MAR-2008**
Amendment number:	**Additional UK Centre, University Hospitals Coventry and Warwickshire**
Amendment date:	**3 November 2010**

Thank you for your letter of 3 November 2010, notifying the Committee of the above amendment.

The Committee does not consider this to be a "substantial amendment" as defined in the Standard Operating Procedures for Research Ethics Committees. The amendment does not therefore require an ethical opinion from the Committee and may be implemented immediately, provided that it does not affect the approval for the research given by the R&D office for the relevant NHS care organisation.

Documents received

The documents received were as follows:

Document	Version	Date
Notification of a Minor Amendment		
Covering Letter	Additional UK Centre, University Hospitals Coventry and Warwickshire	03 November 2010

7.2 Appendix 3: Study Protocol

Short title:

Evaluation of Locking Plating Systems for Distal Femoral Fractures.

Full Title:

A Randomised Controlled Trial of different locking plate fixation systems for Periprosthetic or Osteoporotic Distal Femoral Fractures: Polyaxial Locked Plating System (POLYAX plate, DePuy) vs. Less Invasive Stabilisation System (LISS plate, Synthes) - a pilot study.

Keywords:

Randomised controlled trial; Multicentre; Distal Femoral fractures; Supra/Intercondylar femoral fractures; Periprosthetic fractures; Osteoporotic fractures; Open reduction internal fixation; Plate Fixation; Locking Plates.

PRIMARY INVESTIGATION SITE: Academic Department of Trauma and Orthopaedics, Leeds Teaching Hospitals, School of Medicine, University of Leeds

Funding Organisation: DePuy, International Ltd

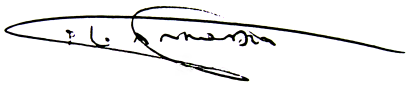
Protocol Date: 18 JUL 2008

Protocol: version 8.0 – 18-JUL-08

SIGNATURE PAGE

A Randomised Controlled Trial of different locking plate fixation systems for Periprosthetic or Osteoporotic Distal Femoral Fractures: Polyaxial Locked Plating System (POLYAX plate, DePuy) vs. Less Invasive Stabilisation System (LISS plate, Synthes) - a pilot study.

By signing below, the Investigator agrees to adhere to the protocol as outlined. This study will be conducted in accordance with ISO 14155, the Declaration of Helsinki, the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines, and local ethical and legal requirements.



___ Prof PV Giannoudis _____ ____20JUL2008____

Investigator's Signature Date

____ Mr NK Kanakaris _____ _____20JUL2008___

Investigator's Signature Date

TABLE of CONTENTS

PAGE

CLINICAL INVESTIGATION PLAN SUMMARY

TITLE	**A Randomised Controlled Trial of different locking plate fixation systems for Periprosthetic or Osteoporotic Distal Femoral Fractures: Polyaxial Locked Plating System (POLYAX plate, DePuy) vs. Less Invasive Stabilisation System (LISS plate, Synthes) - a pilot study.**
SPONSOR	Academic Department of Trauma and Orthopaedics, Leeds Teaching Hospitals, School of Medicine, University of Leeds
FUNDING Organisation	DePuy International Ltd
PRIMARY INVESTIGATION SITE	**Academic Department of Trauma and Orthopaedics, Leeds Teaching Hospitals, School of Medicine, University of Leeds**

OBJECTIVES	The Primary objective of this Pilot study is to produce preliminary evidence on the union incidence and time to union of two different plating systems in the clinical setting of periprosthetic or osteoporotic distal femoral fractures, in preparation of a subsequent power analysis of future larger study / studies on the same subject. The Secondary Objectives of this investigation are: • Record and compare the intraoperative details of the use of the two Plating Systems (length of incision, closed / open reduction, duration of the operation) • Record and compare the malunion rates between the two Plating Systems at the clinical setting of periprosthetic fractures or osteoporotic fractures of the distal femoral metaphysis. • Record and compare the hardware failure rates between the two Plating Systems at the clinical setting of periprosthetic fractures or osteoporotic fractures of the distal femoral metaphysis • Record and compare the incidence of intra- and post-operative early and late complications and secondary interventions between the two Plating Systems at the clinical setting of periprosthetic fractures or osteoporotic fractures of the distal femoral metaphysis. • Record and compare the functional outcome and patient quality of life between the two Plating systems as this is recorded by the Oxford Knee Score the American Knee Society score and the patient-completed EuroQol EQ-5D. These evaluations will be obtained at all evaluation points. • Evaluate the feasibility of performing protocol procedures in preparation for a pivotal study.
INDICATION	Periprosthetic femoral fractures around knee prosthesis Osteoporotic fractures of the distal femur
CLINICAL INVESTIGATION DESIGN	CLINICAL PHASE IV Pilot study
NUMBER OF SUBJECTS	60
TARGET POPULATION	Patients presenting with a periprosthetic or osteoporotic distal femoral fracture
LENGTH OF CLINICAL INVESTIGATION	24 months

TEST DEVICE/PROCEDURE	Polyaxial Locked Plating System (POLYAX plate, DePuy, Warsaw, Indiana)
COMPARATOR	Less Invasive Stabilisation System (LISS plate, Synthes - Synthes GmbH Glutz Blotzheim-Str. 1-3, 4500 Solothurn, Switzerland, Tel. +41 32 720 40 60, Fax +41 32 720 40 61)
SAFETY	Adverse events will be recorded and reported appropriately throughout the investigation to assess safety.

INVESTIGATIONAL SCHEDULE

Assessment Time points		**Baseline**	**4 weeks post-op**	**3 months**	**6 months**	**9 months**	**12 months**
1	Clinical Examination	**x**	**x**	**x**	**x**	**x**	**x**
2	EuroQol EQ-5D	**x**	**x**	**x**	**x**	**x**	**x**
3	AKSS		**x**	**x**	**x**	**x**	**x**
4	OKS	**x**	**x**	**x**	**x**	**x**	**x**
5	VAS pain (hip thigh knee)	**x**	**x**	**x**	**x**	**x**	**x**
6	Xrays (AP-Lateral)	**x**	**x**	**x**	**x**	**x**	**x**
7	CT Optional in case of suspicion				**(x)**		**(x)**

	of non-union						
8	Hematology Tests	**x**					
9	Biochemistry Tests	**x**					

1. INTRODUCTION

1.1 Periprosthetic Fractures of Distal Femur – Background

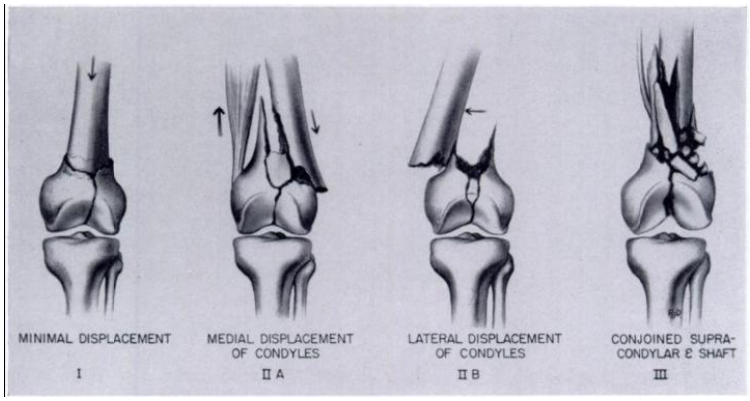
Fractures approximating the femoral component of a total hip or knee reconstruction are described as periprosthetic femoral fractures. They occur in 0.1% to 6% of all arthroplasty patients.[1-4] The increase of the total elder population, the rapidly rising rates of knee and hip arthroplasties, and the expansion of the age range of the treated population, are all expected to boost even further the total number of periprosthetic fractures.[5]

Displaced periprosthetic fractures of the distal part of the femur proximal to a stable total knee replacement are infrequent, and represent a challenging surgical problem.[3,5-12] The reported prevalence is 0.3% to 2.5%, but these percentages are expected to increase because of the increased numbers of total knee replacements being performed, and the increasing longevity of patients.[1,3,5-13]

Conventional treatment options include bed rest; traction and cast immobilization; operative fixation with Rush rods, supracondylar nails, compression plates, external fixation frames, with or without bone-grafting; and revision arthroplasty with a long-stem prosthesis.[3,11,14,15] However, the reported complication rates of these complex fractures range from 19 to 25%.[12,16]

The modified Neer classification[10] (**Figure 1**) is mostly used for PFF around knee prosthesis.[17]. Early classification systems focused on displacement as a major indication for either surgical or non-surgical management. According to most of the established algorithms of treatment, the different types of PFF require certain methods of intra- or extra-medullary fixation, grafting, implant revision, or combinations. However, recent techniques and current implants have made surgical management preferable for most periprosthetic fractures. The fracture configuration and location, implants stability and patients bone stock are estimated and dictate the treatment alternatives.[2,12,18]

(Figure 1)



The successful outcome of these challenging fractures is directly associated to the implant stability, the union of the fracture site, and the minimizing of the period of restricted mobilization.[2,12,18] The implant stability has been classified according to the Rorabeck[11] scheme in 3 types (Type I: fracture undisplaced, prosthesis intact, Type II: fracture displaced, prosthesis intact, and, Type III: fracture undisplaced or displaced, prosthesis loose), and have been utilized from different investigators.[19]

1.2 Osteoporotic Fractures of the Distal Femur – Background

Osteoporosis, a systemic progressive disease affecting mainly the aging population, is responsible for significant morbidity and mortality due to fractures and their complications.[20] About 30% of fractures in men, 66% of fractures in women and 70% of inpatient fractures are potentially osteoporotic. The epidemiology of adult fractures is changing quickly. Among the 10 most frequent sites of fractures related to osteoporosis is also the distal femur.[21-23]

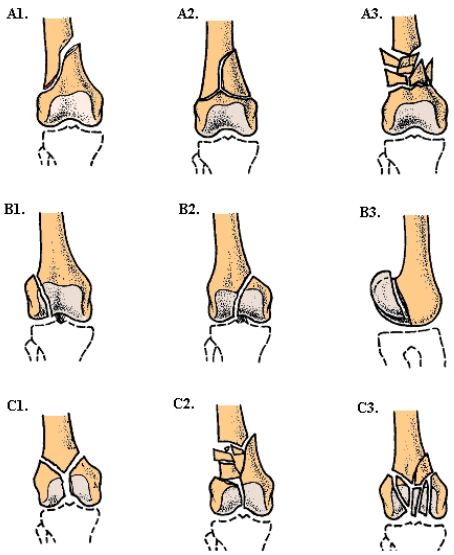
However, fractures of the distal femur are rather infrequent (6.3% of the total number of femoral fractures according to the AO classification), but the incidence is increasing. Distal femoral fracture, historically have been difficult to treat. The distal

fragment is short, and options for fixation often are limited because of the concurrent presence of lag screws, coronal fracture planes or even implants in the case of PFFs. Any

internal fixation device must provide coronal plane stability to maintain correct alignment during healing and all this with the additional intricacy of the decreased bone density and the often inadequate hold of any applied screws.[24-29]

The most eligible classification system of distal femoral fractures is that of the AO-OTA group. It applies also for the osteoporotic fractures of this site. (**Figure 2**)

Figure 2



Osteoporosis grossly can be identified from plain xrays of the proximal femur by using the Singh index.[30] Besides its weaknesses is the only easy to apply osteoporosis index that does not need additional diagnostic imaging or methods than the standard AP xray of the Hip. This index (grade 1-6) is often used at the clinical practice to define the presence of osteoporosis (grade <4) also in cases of distal femoral fractures since an AP

view of the proximal femur is also acquired during the standard investigations of a distal femoral fracture periprosthetic or not.

1.3 Internal Fixation – Plate Fixation

Treatment of distal femoral fractures or else supra- or intra-condylar femoral fractures consist a significant challenge for the orthopaedic trauma surgeon. In those cases that they refer to the elderly population the difficulties are increased due to the potential comorbidities of the patient, the concurrent osteoporosis, or the presence of adjacent knee prosthesis. Internal fixation is the nowadays the gold standard of treatment especially if the arthroplasty component is stable.

Since 1960 and thanks to improvements in the engineering design of implants, more clinically oriented fracture classifications, the development of surgical and anaesthesiological techniques, and the use of prophylactic antibiotics, most distal fractures of the femur can be treated by open reduction and internal fixation.[31-33] Furthermore, during the seventies, one of the most commonly used implants for this purpose was a 90° angled blade plate, the condylar plate (CP). The CP has become less popular since the introduction of newer implants[34,35], i.e. the so-called screw plates, which are technically easier to insert and produce comparable clinical results.[36,37] The gold standard of this new generation of implants for the distal femur has undoubtedly been the Dynamic Condylar Screw (DCS).[34,38]

With first generation plates such as the DCP (Dynamic Compression Plate), the potential compromise of blood supply to the bone was a drawback. Thus, LC–DCP plates (Limited Contact – Dynamic Compression Plate) were designed. The undersurface of these plates has a reduced area of contact to the bone and appears to preserve the blood supply.[39]

With the latest generation plates, the LCP (Locking Compression Plate), the screws can be locked into the plate to form a stable construct.[40] These plates no longer need to be pressed against the underlying bone, and blood supply to the bone is least disturbed, enabling the fracture to heal faster. Additionally this construct of locking of the screws to the plate allows for a biomechanically safe insertion of unicortical screws.[41]

Traditional unicortical bone screws have lower load carrying capability than bicortical screws. By locking the screws into the plate, a fixed-angle construct is created that is much less prone to loosening or toggle than traditional non-locked plates.[42] This locked screw-plate connection provides the path for load transmission to the plate.

The latest entries in the promising field of locking plate devices, the LISS-Synthes and the POLYAX-DePuy plates, offer significant theoretical advantages for the treatment of supracondylar femur fractures associated with a total knee arthroplasty (TKA). These devices also can be inserted with relative ease by using minimally invasive techniques, provide a fixed angle construct, and improve fixation in osteoporotic bone.[43] They are extramedullary, internal fixation systems that have been developed to incorporate the modern advances in the area of extramedullary force carrier like those of indirect reduction, minimal implant-bone contact, development of internal fixators in order to limit soft tissue disruption and preserve the blood supply.

The LISS plate (Less Invasive Stabilization System) (SYNTHES - Synthes GmbH Glutz Blotzheim-Str. 1-3, 4500 Solothurn, Switzerland, Tel. +41 32 720 40 60, Fax +41 32 720 40 61)[44] was originally designed for the distal femur and proximal tibia. Its shape conforms to the anatomical contours of the specific area of the bone. Its instrumentation is designed so that instead of making a long incision to place the plate against the bone, it can be introduced through a small cut. Thus, the traditional concept of internal fixation, which requires an extended approach to the fracture zone, is presently challenged by a more biological, atraumatic approach with careful handling of the soft-tissues.[45-49] Large published series of periprosthetic fractures around total knee arthroplasties treated with LISS plates documented satisfactory union rates ranging from 86%[50] to 100%.[51]

The POLYAX Locked Plating System (DePuy, Warsaw, Indiana)[52] is designed to give the surgeon maximum flexibility with the use of fixed-angle locking, variable-angle locking and non-locking screw options. The result is fracture fixation based on each individual patient's fracture type, bone quality and anatomy. The system is indicated for

use in open or percutaneous fracture fixation cases requiring Open Reduction Internal Fixation (ORIF) of closed and open fractures of the distal femur and proximal tibia, including repair of nonunions and malunions.[7,42]

1.4 Need for a Definitive Randomised Controlled Trial

The current opinion among orthopaedic surgeons supports the use of locking plate systems, with or without supplementary augmentive techniques, for internal fixation of these fractures. However no scientific evidence comparing these different systems of locking fixation exists. The theoretical advantage of multiaxial locking of the screws to the distal femoral metaphysis, and its user-friendly concept deserves attention and requires scientific proofs.

2. STUDY OBJECTIVES

The present study is a pilot study aiming in providing preliminary evidence on the use of two different plating systems on the particular clinical environment described in the protocol. The proposed pilot study will identify and validate the primary end points, will provide data for sample-size calculations, and will define "successful treatment" criteria in this particular clinical setting. This evidence will facilitate a robust design of the subsequent randomised trial of adequate sample size to identify statistical significant differences.

The primary objective of this pilot study will be to test the hypothesis that osteosynthesis with the polyaxial plating system of periprosthetic or osteoporotic fractures of the distal femoral metaphysis achieves similar union rates, at comparable time frames with the LISS plating system. Because the present study represents a pilot one, it is anticipated that it will produce preliminary evidence and the necessary data for a subsequent power analysis of future larger study / studies of the same subject.

The secondary clinical outcomes include:

1) Comparison of the intraoperative details of the use of the two implants (length of incision, duration, closed / open reduction, estimated blood loss)
2) Comparison of the incidence of malunion between the two Plating Systems at the clinical setting of periprosthetic fractures or osteoporotic fractures of the distal femoral metaphysis.
3) Comparison of the incidence of hardware failure and secondary interventions between the two Plating Systems at the clinical setting of periprosthetic fractures or osteoporotic fractures of the distal femoral metaphysis
4) Comparison of the incidence of intra- and post-operative early and late complications between the two Plating Systems at the clinical setting of periprosthetic fractures or osteoporotic fractures of the distal femoral metaphysis.
5) Comparison of the functional outcome and patient quality of life between the two Plating systems as this is recorded by the Oxford Knee Score[53] and the patient-completed EuroQol EQ-5D[54]. These evaluations will be obtained at all evaluation points.
6) Comparison of the radiological findings between the two plating systems in terms of screw positioning and projection.

3. DEVICES

3.1 Investigational Fixation System – POLYAX Locked Plating Systems[52]

The POLYAX™ Locked Plating System is indicated for the treatment of distal femur and proximal tibia fractures. The system is intended for use in open or percutaneous fracture fixation cases requiring Open Reduction Internal Fixation (ORIF) of closed and open fractures of the distal femur and proximal tibia, including repair of nonunions and malunions.

The POLYAX Locked Plating System is designed to give the surgeon maximum flexibility with the use of fixed-angle locking, variable-angle locking and non-locking screw options. The result is fracture fixation based on each individual patient's fracture type, bone quality and anatomy. The POLYAX femoral and tibial plates are designed for placement on the lateral side of the distal femur and proximal tibia, respectively, and are pre-contoured to closely match the anatomy of the bones.

The POLYAX Locked Plating System is intended for use in:

- Periarticular fractures
- Periprosthetic fractures
- Malunions
- Non-unions
- Osteotomies

Each plate is manufactured from TiMAX™ anodized titanium alloy Ti-6Al-4V, which gives the plates superior fatigue strength, excellent biocompatibility and optimal stress transfer. The screws are manufactured from color-anodized titanium alloy Ti-6Al-4V for easy identification and selection in the operating room (OR). All instruments are color-coded in accordance with associated color-anodized screws to enhance surgical efficiency. The system includes a handle and radiolucent target guide that connects to the plate for minimally invasive plate and screw insertion, as well as several tools to aid in fracture reduction.

Screw locking is accomplished either by threading a screw directly into the plate (fixed-angle construct) or into a patented polyaxial bushing (variable-angle construct) contained within the plate. The screw's locking portion consists of a triple-lead, tapered-thread on the screw head, which is designed to engage the plate or bushings. The bushings allow the surgeon to lock screws in place at a desired angle within a maximum 30-degree cone of angulation. Non-locking screws are provided for placement in either a fixed-angle locking hole or polyaxial bushing.

Distal locking of the femoral POLYAX Locked Plating System construct is accomplished by one centrally located 8.0 mm fixed-angle locking screw surrounded by

four 5.5 mm polyaxial locking bushings. The proximal plate stem has threaded holes for 4.5 mm fixed angle locking or 4.5 mm non-locking screws and is anatomically contoured to match the femoral bow. Plates are available in lengths of 6, 9, 12, 15 and 18 holes (Cat. No. 8141- 30-1XX—right, Cat. No. 8141-31-1XX—left). The plate has three K-wire holes for optional intra-operative temporary fixation.

3.2 Investigational Fixation System – LISS plate[44]

The Less Invasive Stabilization System (LISS) is an extramedullary, internal fixation system that has been developed to incorporate technical innovations. Its main features are an atraumatic insertion technique, minimal bone contact, and a locked, fixed-angle construct.

The LISS Plating System is intended for fixation of fractures in the distal femur:

• Extra-articular or distal diaphyseal fractures

• Complete intra-articular fractures including those with associated coronal fractures

• Periprosthetic fractures

System Features

- Unicortical locking screws offer angular stability for optimal purchase and reduced stress on the bone.
- Locking screws perform drilling, tapping and locking to the plate.
- Anatomic shape of the plate and locked construct makes intraoperative contouring unnecessary. Percutaneous, submuscular insertion of the plate does not disrupt the cortical blood supply.

Optimized screw position in the condyles to avoid intercondylar notch and Patellofemoral joint and maximize bone purchase.

Published series of LISS plating for distal femoral periprosthetic fractures around knee arthroplasty implants or osteoporotic fractures. Kregor et al[55] used LISS plates to

stabilise 13 distal femoral periprosthetic fractures above knee prostheses and reported overall complication rates of 15.4% and union rates of 84%.

At a similar series O'Toole et al[51] reported on 2006 upon a series of 11 patients with fractures occurring above knee prostheses with the LISS plate. They concluded favorably, as there were no complications in this group of patients especially when these were compared with the results of Su et al[12] (19% overall complication rate), who summarized the literature on operative treatment of these fractures.

Ricci et al[50] the same year published their prospective case series of 22 patients with 24 (2 bilateral) supracondylar femur fractures above a well-fixed non-stemmed TKA treated with the LISS plate. At an average of 15 (range, 6-45) months of follow up, 19 of 22 fractures healed after the index procedure (86%). Healing complications occurred in 16% (2 cases developed infected nonunions and 1 an aseptic nonunion). Postoperative alignment was satisfactory (within 5 degrees) for 20 of 22 fractures. Hardware failures occurred in 4 cases (fracture of screws). Fifteen of 17 patients who healed returned to their baseline ambulatory status, with 5 requiring additional ambulatory support compared with baseline.

4. INVESTIGATIONAL PLAN

4.1 Study Design

This pilot study is designed as a multicenter concealed randomised controlled trial. Patients will be enrolled at **4 (four)** institutions. Senior Orthopaedic Surgeons will use one of two locking plating systems in 60 patients who have sustained a distal femoral osteoporotic or periprosthetic fracture around a knee arthroplasty (DFF).As this study is a "pilot" it is expected to produce adequate scientific evidence of the current clinical practice of these two plating systems in order to facilitate the power analysis and the designing of larger survey that would test the effectiveness of the different methods of fixing these types of fractures.

Patients diagnosed with a periprosthetic around a total knee arthroplasty with non compromised-stable femoral component (modified Neer type I, III), or with an osteoporotic fracture of the distal Femur will be recruited through the medical institutions of the participating Investigators. Either periprosthetic or osteoporotic distal femur fractures will not be considered separately and the endpoint will be the number of 60 patients altogether.

The two equal groups are defined as:

Group A: 30 DFF treated operatively with a ***POLYAX plate*** (Polyaxial Locked Plating System – DEPUY).

Group B: 30 DFF treated operatively with a ***LISS plate*** (Less Invasive Stabilisation System – SYNTHES).

Study enrolment will be completed upon successful treatment of 60 patients. All treated patients will be followed for 12 months after initial surgery.

All the patients will be assessed at 1 month, 3 months, 6 months, 9 months, and 1 year post-operation which is the standard follow-up schedule of such cases.

4.2 Multi-centre organisation

The Primary Site of Investigation (SI) will be the Academic Department of Trauma and Orthopaedics, Leeds Teaching Hospitals, School of Medicine, University of Leeds. The Primary Investigator (PI) will be the head of the later, Professor Peter V. Giannoudis. The co-Investigators will be Consultant Orthopaedic Surgeons at each of the different Investigation Sites (SI) of the study.

A total of 4 trauma centres would be invited to participate in the trial. Each centre would have to recruit and follow up on average 15 patients for a period of 12 months. No upper limit of recruited patients for each centre will be used in order to reach the target number of 60 recruited patients.

Recruitment of the 4 centres-Investigation Sites will be completed in the first 3 months from the initiation of the study at the Primary Investigation Site. Initiation of the study at each of the Sites will be completed within this time frame of the 3 months.

4.3 Randomisation Process

Randomisation will be performed centrally using a ballot system as the previous method via the Clinical Trials Research Unit's (CTRU) automated randomisation system, cannot support the out of hours service required for a clinical trial involving trauma patients. Patients will randomly be allocated into one of two study groups, for fixation with either POLYAX or L.I.S.S Plating sytems.

4.4 Blinding

The Subject will be blinded to the treatment assignment. On the day of surgery, surgeons and study staff will be blinded to the treatment assignment of the patient until the communication with the research fellow, who will perform the ballot randomisation and assignment of each case to one of the two study groups.

It should be ensured that the healing outcome assessors who will perform the radiological examination at follow-up will not be privy to the subject's case notes, to help maintain the blinding. For this reason as far as possible the x-rays and the CTs will be stored and assessed separately.

4.5 Withdrawals Prior to Randomisation

On the day of surgery, each patient will be assigned to one of the two treatment groups (POLYAX or LISS). Any patient enrolled but not randomised will be assigned a patient number (similar to the process described above) but not a randomisation number. The reason for failure to randomise will be recorded on his/her CRF.

If an intraoperative decision is made to perform a procedure other than what was intended for study enrolment the subject will be considered a withdrawal. If a randomised patient is withdrawn prior to treatment, the next patient will be assigned the next randomly determined treatment as per the study randomisation plan.

For enrolled patients who are not randomised, the following information will be recorded on the CRF if available:

- Demographic information
- Baseline vital signs
- Inclusion/exclusion criteria
- Completion/discontinuation
- Preoperative clinical laboratory evaluation

4.6 Duration of the Study

It is anticipated that the entire study will take approximately 42 months to complete. Patient enrolment is expected to take 30 months. Each patient treated by either of the internal fixation methods will participate in the study for 12 months (including baseline, randomisation, treatment and follow-up).

5. SELECTION OF SUBJECTS

Subjects who fulfil the following inclusion and exclusion criteria will be considered eligible to be entered into this clinical investigation.

5.1 Inclusion Criteria

To be eligible for study participation, a subject must meet all of the following criteria:

6. Subject is willing and able to understand, sign and date the study-specific, Institutional Review Board/Ethics Committee approved patient informed consent and applicable privacy regulations.
7. Subject must require surgical treatment of a periprosthetic fracture adjacent to components of a total knee arthroplasty, or of an osteoporotic distal femoral fracture.
8. Subject is skeletally mature (≥18 years of age or radiographic evidence of closure of epiphyses).
9. Subject was able to ambulate satisfactorily prior to the fracture incident.
10. Subject agrees to participate in the post-operative clinical evaluations.

5.2 Exclusion Criteria

To be eligible for study participation, a patient must not meet any of the following criteria:

10. Subject who has a clinically significant organic disease, including cardiovascular, hepatic, pulmonary, neurologic, or renal disease, or established dementia or other medical condition, serious intercurrent illness, or extenuating circumstance that, in the opinion of the Investigators, would preclude participation in the trial or potentially decrease survival or interfere with ambulation or rehabilitation.
11. Subject whose fracture is the result of an infection.

12. Subject with known metabolic bone disease or other condition (other than osteoporosis), which would negatively impact on the bone healing process (e.g. history of Paget's disease or other osteodystrophy).
13. Subject currently being treated with radiation, chemotherapy, immunosuppression, or chronic steroid therapy (prednisone use up to 5 mg/qd or its equivalent is allowed).
14. Subject has other fractures that would interfere with ambulation or rehabilitation.
15. Subject has a condition, which places him/her at risk for osteomyelitis.
16. Subject has an American Society of Anaesthesiologists (ASA) Physical Status Classification greater than 2.
17. Subject has a life expectancy less than 24 months.
18. Subject whose fracture is an open fracture.
19. Subject whose fracture is accompanied with a loosening of the original prosthesis as this is determined preoperatively or intraoperatively (intraoperative exclusion criteria*).

6. INVESTIGATIONAL PROCEDURES

An overview of the procedures each subject will undergo during the course of this clinical investigation is contained in the Investigational Schedule at the front of this CIP and in more detail as follows:

6.1 Informed Consent

All patients in this study are to be completely informed, in accordance with GCPs and local regulatory authority requirements, concerning the pertinent details and purpose of the study including the investigational nature of the product. All foreseeable risks and potential benefits, with might occur with the use of the devices, will be discussed with the patient. All relevant study information is contained in the patient information sheet, which the patient receives prior to written consent for inclusion in the study. In an emergency situation as this study will include this group of patients, all relevant study information will also be conveyed to the patient both verbally and in written form before formal consenting for study participation. The patient will be informed that, should an unanticipated serious adverse device event (SADE) occur, which presents an unreasonable risk to participating patients, he/she will be notified and the study enrolment terminated. The patient will be informed that his/her medical records are subject to review by representatives of the Sponsor, the Ethics Committee and Regulatory Authorities as necessary. Patient confidentiality will be maintained at all times. The patient will be told that he/she is free to refuse study participation or to withdraw from the study at any time without compromising future medical care.

A sample informed consent form will be provided to the investigators. The Sponsor will review the site's draft informed consent before it is finalised, and the final Ethics Committee approved document must be provided to Sponsor. The Ethics Committee – approved written consent form is to be supplied by the Investigators and will be understood and signed by each patient) prior to enrolling in the study. The Investigators are responsible for maintaining each patient's consent form in the study file and to provide each patient with a copy of the consent form.

6.2 Subject eligibility and identification

Once written consent has been obtained, the subject will be allocated to the next available investigational subject number. This number will consist of the site clinical investigation number followed by 01 for the first subject, 02 for the second subject and so on. This number will then become the unique identifier of the subject and will be written

on each page of the Case Report Form (CRF) and all other clinical investigation documentation relating to the subject. The eligibility checklists contained in the CRF will be completed to document adherence to the inclusion and exclusion criteria.

Where a subject fails to fulfil any element of the inclusion and exclusion criteria, this will be documented and the signed patients consent form and completed eligibility checklists retained by the Clinical Investigator. The subject will not be advanced any further into this clinical investigation.

The Clinical Investigator, with the consent of the subject, will also inform the subject's General Practitioner (GP)/Primary Care Physician in writing of the subject's participation in this clinical investigation according to local guidelines.

6.3 Screening Assessment

A complete medical and surgical history will be obtained, including concurrent diseases and previous fractures of any site. Specific information will be recorded on the CRF relating to any prior or existing medical conditions/surgical procedures involving the following categories: Infectious Diseases, Allergic, Metabolic/Endocrine/Nutritional, Haematopoietic, Musculoskeletal, Dermatological, Head, Ears, Eyes, Nose, and Throat (HEENT), Breasts, Respiratory, Cardiovascular, Gastrointestinal/Hepatic, Genitourinary/Renal, Neurologic, and Psychiatric/Psychosocial.

Conditions and/or procedures reported will be compared to the inclusion and exclusion criteria for this study. Specific attention will be paid to the patient's previous history with respect to exclusionary conditions, procedures, and surgeries. Patients will also be questioned regarding their pre-fracture ambulatory status and pre-fracture living situation.

Also;

Demographic data, height, and weight will be recorded at the Baseline visit,

The current Smoking status of the patient will be recorded,

A standard physical examination will be conducted at Baseline,

All concomitant medications will be recorded,

And the following vital signs will be measured at Baseline and all postoperative assessments: oral temperature, blood pressure, and heart rate.

6.4 Baseline Assessments

Baseline assessments will include subject and surgeon evaluations using validated outcome measures. Details of the assessment tools are given below:

6.4.1 Outcome Scores

EuroQol EQ-5D[54]

Outcomes information from the patient-completed EuroQol EQ-5D[54] will be obtained at all evaluation points. This quality of life measure should be completed at each visit independently by the patient and prior to the clinical evaluation.

Oxford Knee score (OKS)[53] and American Knee Society Score (AKSS)[56]

The Oxford Knee score (OKS)[53] and American Knee Society Score (AKSS)[56] will be assessed at all post-operative visits. All investigational sites will be provided with uniform guidelines and specific forms of the two functional outcome scores in order to improve scoring consistency.

Weight Bearing

The weight bearing potential of the affected hip will be evaluated at baseline and all post-operative visits to assess if the joint is non-weight bearing, partial weight bearing or full weight bearing.

Visual Analog Scale[54]

Will be recorded by the patient at all evaluation points through the use of a Visual Analog Scale.[54] The patient will be asked to complete one Visual Analog Scale for the affected limb.

6.4.2 Radiographic Evaluations

Anterior-posterior (AP) and lateral views of the femur and the knee will be taken at all time points. Two independent radiologists will review copies of subject's anteroposterior and lateral radiographs, in order to determine radiographic outcome, e.g.

union/nonunion and alignment. A third independent, blinded to the two previous assessments, radiologist will evaluate those radiographs for which the two radiologists are in disagreement on the determination of radiographic outcome. The third radiological readings should be the deciding evaluation (i.e., majority rules). If after the third radiological reading the radiographic outcome is deemed inconclusive at 6, and 12 months a CT scan will be obtained and used to determine radiographic outcome. This is also the standard method of assessing fracture healing whenever a definite diagnosis cannot be made by plain xrays.

Relevant definitions:

Osteoporosis: Singh index[30] – grade<4 as determined via an AP of the proximal femur.

Union: Disappearance of fracture lines on AP and lateral view or on CT scan if necessary.

Nonunion: Failure of the fracture line to completely obliterate on the AP and lateral views or on CT scan.

Malunion: Shortening >2 cm, Varus or Valgus >10°, Rotational deformity >15°

Hardware Failure: plate or screw breakage or displacement.

6.4.3 Clinical Laboratory Evaluations

At the baseline the following clinical laboratory evaluations will be performed (they are considered as standard pre-operative evaluation tests of patients with such fractures):

• Haematology: Haemoglobin count, White Blood Cell (WBC) count, Hand platelet count.

Biochemistry: Creatinine, , potassium, sodium, ,

, urea and international normalised ration(INR).

Clinical laboratory evaluations will be performed by the standard laboratories of its participating institute. The Investigators are responsible for reviewing and signing all laboratory reports. The clinical significance of each value outside of reference range will be assessed and documented as either not clinically significant (NCS) or clinically significant (CS). All CS values or the diagnosis must be captured as an ADE unless it is due to a pre-existing condition.

Clinical significance is defined as any variation in physical findings that has medical relevance and may result in an alteration in medical care. Clinical laboratory reports will serve as source documents.

6.5 Perioperative Information for the Surgery

For all patients information including the following will be documented on the CRF as soon as possible following the patient's surgery:

• Date of surgery

- Randomisation Information
- Presence, placement location, type, and number of drains placed
- Estimated blood loss during surgery as documented on Anaesthesia Record
- Use and amount of any blood products administered
- Any additional surgical procedures performed during the surgery
- Time of the incision opening and closure
- Modified Neer Classification for periprosthetic fractures

- AO-ASIF classification of distal femoral osteoporotic fractures
  - Determination of the Singh index of the subject (grade <4)
  - Surgical Approach
  - Length of incision(s)
  - Operative Side
  - Requirement for muscle repair or reattachment
  - Type and number screw fixation used
- Reduction performed open or closed

Unforeseen events (findings or procedures) may occur during the internal fixation. These unforeseen events are those that are not planned as part of this surgery (e.g., a drop in oxygen saturation intraoperatively, evidence of an acute myocardial infarction, allergic reaction to the antibiotic, etc.). If such an event occurs the Investigators should reassess the patient for participation in this study.

Surgeons and study staff will be blinded to the treatment assignment of the patient until the randomisation occurs. In addition, the patient will be blinded to his/her randomisation assignment until the 12-month follow-up, or until the time of patient's withdrawal.

6.6 Follow Up Assessments

All follow-up assessments will be recorded in the subject's CRF.

At each follow-up assessment, the following information and procedures will be recorded:

- EuroQol EQ-5D[54]
- Weight Bearing
- OKS[53], AKSS[56] scores
- Radiographic Evaluation: Plain film X-ray (anterior-posterior & lateral).
- Visual Analog Scale[54] for pain of the Hip, Thigh and Knee
- Adverse Events
- Concomitant Medications
- Smoking Status

6.7 Timing of Assessments

Subjects included in the clinical investigation will return for follow-up as shown in the table bellow. The Clinical Investigator, or a member of his investigative team, will perform the follow-up assessments.

Post-operative Time Point	Window for Appointment
4 weeks	± 7 days
3 months	± 14 days
6 months	± 30 days
9 months	± 30 days
12 months	± 60 days

6.8 Withdrawals and Replacements

6.8.1 Reasons for Early Termination

Each patient is free to discontinue from the study at any time, for any reason. If a patient discontinues from the study (regardless of the reason), the Investigators will record the reason for withdrawal on the case report form (CRF). Examples of reasons for premature withdrawal of a patient from the study include:

- Intercurrent illness that would, in the judgment of the Investigator, affect study assessment to a significant degree
- Patient non-compliance with follow-up assessments
- Patient request to withdraw
- Patient lost to follow-up
- Termination of the study by the Sponsor
- Other (reason to be documented in the CRF)
- Death

Every effort shall be made to have withdrawn patients return for the required fracture healing evaluation as detailed in the protocol.

6.8.2 Replacements

If an intraoperative decision is made to perform a procedure other than what was intended for study enrolment the subject will be considered a withdrawal. If a randomized

patient is withdrawn prior to treatment, the next patient will be assigned the next randomly determined treatment as per the study randomisation plan.

6.8.3 Study Discontinuation

If the Sponsor, Investigators, Research and Development (R&D) and Medicines and Healthcare products Regulatory Agency (MHRA) monitoring authorities discover conditions during the study that indicate that the study or study site should be terminated, this action may be taken after appropriate consultation between the Sponsor, Investigator, and R&D and MHRA authorities. Conditions that may warrant termination of the study of the study site include, but are not limited to:

- The discovery of any unexpected, serious, or unacceptable risk to patients enrolled in the study,
- The decision on the part of the Sponsor to suspend or discontinue testing, evaluation, or development of the investigational product,
- Failure of the Investigators to comply with GCP guidelines,
- Submission of knowingly false information from the research facility to the Sponsor, Clinical Monitor, or regulatory authorities,
- Insufficient adherence to protocol requirements.

In the event of early study termination for any reason, study personnel at the study site will prepare a list of all patients discontinued from the study after enrolment along with a patient identifier, the specific reason for discontinuation, dosing information the elapsed time postoperatively before discontinuation, and documentation of all treatment emergent adverse events.

7. REGULATORY AND REPORTING REQUIREMENTS

7.1 Adverse Event and Serious Adverse Events Definitions

The Investigators are responsible for monitoring the safety of patients who have entered the study.

As an adverse event involving a device (ADE) is defined any undesirable clinical occurrence in a subject whether it is considered to be device-related or not.

As a serious adverse event involving a device (SADE) is defined as any ADE that:

4. led to death
5. led to a serious deterioration in the health of the subject that resulted in life threatening injury or illness; resulted in a permanent impairment of a body structure or function; required in-patient hospitalisation or prolongation of existing hospitalisation; or resulted in medical or surgical intervention to prevent permanent impairment to body structure or body function;
6. led to fetal distress, fetal death or congenital abnormality or birth defect.

Patients will be instructed to report any ADE that they experience to the Investigator.

7.2 Adverse Event Relationship

The relationship of an adverse event to investigational fixation system is to be assessed according to the following definitions:

Definite: There is a clear-cut temporal association, and no other possible cause.

Probable: A clear-cut temporal association and a potential alternative aetiology are not apparent.

Possible: There is a less clear temporal association; other etiologies are also possible.

Unlikely: The temporal association between the ADE and the investigational product, and the nature of the event is such that the investigational product is not likely to have had any reasonable association with the observed illness/event (cause and effect relationship improbable but not impossible).

Not Related: The ADE is completely independent of the investigational product administration and/or evidence exists that the event is definitely related to another aetiology.

7.3 Adverse Device Events (ADE) / Serious Adverse Device Events (SADE) reporting

Investigators will assess ADE at each visit. All adverse events (AEs) occurring, or worsening, after initiation of internal fixation (screw placement) will be considered treatment-emergent. Only treatment emergent adverse events will be captured on the CRF and followed until their resolution or stabilization, or until 30 days after the last patient's end of study visit.

The Clinical Investigator should institute appropriate therapeutic and follow-up measures in accordance with good medical practice but should notify the Co-ordinating Centre of such actions and record them in the subject's CRF. A full written report of the event must be forwarded to the relevant manufacturer within 10 working days of the discovery.

Any ADE, whether or not it is related to the investigational product, is to be reported on the ADE form along with the date and time of onset, severity, and relationship to the study treatment , action taken, and the outcome. To capture the most potentially relevant safety information during a clinical trial, it is important that Investigator record accurate ADE terms on CRFs. Wherever possible, a specific disease or syndrome rather than individual associated signs and symptoms should be identified by the Investigators and recorded on the CRF. However, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the Investigator, it should be recorded as a separate ADE on the CRF.

7.4 Medications

A medication is considered concomitant if it is taken at any time after signing the Informed Consent Form up to and including the 12-month follow-up visit. Medications that have been directly shown to have an effect on bone healing and union rates, such as steroids, NSAIDS, biphosphonates, etc, are of particular interest. Data on medications will include: name, dose, route, regimen, start date, stop date, and indication. At each study visit, the patient will be asked about any additional medications. Concomitant medications taken for the management of the patient's normal postoperative pain should be collected with an indication of "postoperative pain." This will indicate that this is not an ADE for the patient. Anaesthesia medications (induction/reversal) will not be recorded throughout the study. Medications other than antibiotics and pain medications - NSAIDs administered while the patient is in the recovery room after the internal fixation surgery do not need to be recorded *unless they are given for an ADE*. If a patient is medicated or receives other non-drug therapy for an abnormal clinical significant laboratory evaluation (unless this is standard of care or for a pre-existing condition), this will be recorded as an ADE.

7.5 Events Related to the Surgical Procedure(s)

The patients entering this trial are being admitted to the hospital for the purpose of surgery for internal fixation of their periprosthetic or osteoporotic distal femoral fracture. By definition, they will experience a change in their baseline medical status. The following are normally expected consequences of this surgery and will not be considered or recorded as ADEs in this study unless in the judgment of the Investigator the event is considered unusual or of greater severity than expected, or prolongs hospitalization:

- Nausea and/or vomiting within 5 days following surgery
- Temperature rise less than or equal to 100.5 ºF (38.1ºC) (within 48 hours following surgery)

- Postoperative pain (e.g., knee pain) with an onset within the first 5 postoperative days, if assessed by the Investigator to be consistent with the surgical procedure (i.e., internal fixation)

NOTE: Postoperative pain with an onset after the first 5 postoperative days will be recorded as an ADE. Postoperative pain deemed by the Investigator to be of unusual severity or duration, regardless of onset date, will be recorded as an ADE.

8. Data Management

8.1 Statistical Analysis

The analysis of the accumulated data will be a Logistic Regression of Union on covariates that will include use of either Plating system. Such variables will be considered as: age, sex, smoking status, mechanism of injury, type of fracture (AO-ASIF classification of distal femur fractures – 33A/B/C, value of Singh osteoporosis index), period of non-weight bear (NWB), time to partial-weight bear (PWB), time to full-weight bear (FWB), complication rates, Quality of life score – EuroQol 5, knee functional outcome scores (OKS, AKSS).

8.2 Data Quality Assurance

The CRFs will be reviewed at the study site for completeness by a clinical monitor from the Sponsor or designees, and returned to the Sponsor or designees for data management and analysis. If necessary, the study site will be contacted for corrections and/or clarification. All data will be entered into a study database for analysis and reporting. Any data captured electronically (e.g., routine laboratory data) will be electronically transferred into the database. Upon completion of data entry, the database will receive a quality assurance (QA) check to ensure acceptable accuracy and completeness

9. INVESTIGATORS REGULATORY OBLIGATIONS

9.1 Ethical Conduct of the Study

This study will be conducted in accordance with the ethical principles originating from the Declaration of Helsinki, GCP, the ICH guidelines, and local ethical and legal requirements.

9.2 Ethics Committee Approval

The approved protocol, patient information leaflets and informed consent form, for this study must be reviewed and approved by an appropriate, duly constituted IRB/EC prior to enrolment of participants into the study. A letter documenting the IRB/EC approval that specifically identifies the protocol by title must be received by the Sponsor or its representatives prior to the initiation of the study (i.e., prior to shipment of investigational materials to the investigative site). Amendments to the protocol will be

subject to the same requirements as the original protocol, with the exception of administrative amendments. Any amendment containing major modifications (particularly if it may involve an increased risk to the patient) will be approved by the IRB/EC before it may be implemented.

9.3 Pre-Study Documentation

The Investigators must provide the Sponsor with the following documents BEFORE the enrolment of any patients at his/her site:

- Completed and signed Investigator Agreement
- Signed and dated current curricula vita for the Principal Investigator and any/all Sub-Investigators
- Current medical license for the Principal Investigator and any/all Sub-Investigators

• EC-approval for study protocol

• EC-approved informed consent form

• Membership roster for IRB/EC committee that reviewed the protocol and associated documents

• Copy of the protocol signature page signed-off by the Principal Investigator (PI)

• Delegation of Authority form

9.4 Protocol Adherence

The Investigators must read the protocol thoroughly and must follow the instructions exactly. Any change should be agreed to by prior discussion between the Sponsor and the Investigators, with written protocol amendments made prior to effecting the changes agreed upon. The Investigators are not to conduct any protocol modifications without prior written permission from Sponsor.

The Investigators are responsible for enrolling only those patients who have met protocol eligibility criteria.

9.5 Adverse Event Reporting

The Investigators agree to report all adverse events to Sponsor as described in Section 8.3. The Investigators is further responsible for ensuring that any Co-Investigators or Sub-Investigators promptly brings serious adverse events to the attention of the Principal Investigator. The Principal Investigators is also responsible for informing the participating EC of any serious adverse events.

9.6 Case Report Forms

The Investigators must maintain detailed records on all study patients. Data for this study will be recorded in the patient's chart and transcribed from source documentation onto the CRFs. They should be filled out completely by examining personnel or the study coordinator. The CRFs are to be reviewed, signed, and dated by the Investigator. All data on these CRFs should be recorded completely and promptly. A complete CRF copy will remain at the investigational site.

9.7 Permission to Review Source Documents

Investigators must keep accurate separate records (other than the CRFs) of all patients' data, being sure to include all pertinent related information. Any and all adverse events must be thoroughly documented. The Investigators will permit authorized representatives of Sponsor, and the respective national or local health authorities to inspect facilities and records relevant to this study. The Sponsor (or its representatives) or the investigative site must notify the other within two weeks of notification by Regulatory authorities of a potential audit.

9.8 Amendments to the Protocol

No change in the study procedures, except to eliminate an immediate patient risk, shall be effected without the mutual agreement of the Investigator and the Sponsor. All changes must be documented by signed protocol amendments. If changes to the design of the study are made, the amendment must be submitted to and approved by the IRB/EC, signed by the Investigator, and returned to Sponsor and sent to and approved by the appropriate regulatory authorities.

9.9 Change in Investigator

If the Investigators retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the medications.

10. REFERENCES

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7.3 Appendix 4: Patient information sheets & consent forms

PATIENT INFORMATION SHEET

Full Study Title:

A Randomised Controlled Trial of different locking plate fixation systems for Periprosthetic or Osteoporotic Distal Femoral Fractures: Polyaxial Locked Plating System (POLYAX plate, DePuy) vs. Less Invasive Stabilisation System (LISS plate, Synthes) - a pilot study.

Summarised Title:

A Pilot study to compare two different fixation systems of distal femoral fractures in the presence of osteoporosis or adjacent to the prosthesis of a total knee arthroplasty.

Dear Patient,

You are invited to take part in a Pilot research study. Before you decide to take part it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully. Talk to others about the study if you wish.

• **Part 1** tells you the purpose of this study and what will happen if you take part.

• **Part 2** gives you additional information about the conduct of the study.

Please 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?

Your doctor has invited you to take part in this pilot research study to collect information on the existing methods of treating surgically and fixing a certain type of fracture.

The aim of the study is to collect preliminary scientific evidence and to compare the results and the efficacy of two different plating systems. Both plating systems are already in surgical use for distal femoral fractures.

This study aims to collect adequate scientific evidence of the current clinical practice and will be conducted before a complete larger survey that would test the effectiveness of the different methods of fixing these types of fractures.

The study objectives are to compare two equal groups of patients (**20 patients for each group – 40 patients in total**) with similar types of fractures that will be treated with one of the two different plates. The comparison will be focused the healing rates of the fractures, the rates of implant- and fracture-related complications (like delayed healing, non-healing, metalwork failure), and also the functional outcome of the patients after one year from surgery.

2) WHICH ARE THE STUDY-RELATED PLATING SYSTEMS?

The two plating systems that will be compared as to their results are the “Polyax” plate (product of the DePuy Company) and the “LISS” plate (product of the Synthes Company). Both plating systems represent the last generation of plates, which are called “locking plating systems”. Plates and screws are a standard method of stabilising fractures and have many applications in orthopaedic surgery. These particular plates have been designed specifically for the anatomical site of the distal femur (lower part of

the thigh bone – close to the knee). Besides their special design that follows the anatomy of this particular area of the body, both of these plating systems are also "Locking" plates (the screws and the screw holes of the plates and the heads of the screws are threaded and so the screws are steadily engaged and locked to the screw holes of the plates. This characteristic of these plates is considered really helpful and is preferred in cases of osteoporotic bones (weaker than the normal bone).

Both companies represent two of the most reliable and large orthopaedic implant producers of the world. Both implants are already available and in clinical use for at least 5 years now.

3) WHY HAVE I BEEN CHOSEN?

You have been chosen as you have a fracture in the distal femur and you require surgery in order to reduce and stabilise appropriately your fracture. Additionally there is evidence of osteoporosis, or you have an implant of a total knee arthroplasty close to the area of your fracture.

These are the basic characteristics of eligible patients for the present multicentre scientific pilot study. It is anticipated that **60** patients with similar fractures of yours will participate in different clinics in the UK and the rest of Europe.

4) DO I HAVE TO TAKE PART?

No. It is up to you to decide whether or not you take part. If you do, you will be given this information sheet to keep and asked to sign a consent form agreeing to your participation in the study. You are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part will not affect the standard of care you will receive. If you decide not to take part, or you decide to leave the study at any time, your doctor will discuss appropriate alternatives for your care with you.

If you do withdraw, for whatever reason, you will be asked to attend a final study visit for your own safety (which will be similar to your usual clinic visits).

5) WHAT WILL HAPPEN TO ME IF I TAKE PART?

Your participation will last at a maximum of 12 months, and will comprise of a screening interview (at your present hospitalisation and after you sign the consent form), surgery, interview at the day of your discharge, and of a series of follow-up appointments at the outpatient fracture clinics at 1 month, 3 months, 6 months, 9 months and 1year after the day of your surgery.

A series of study-specific documents will be filled from your doctor and the study-related personnel at this department. They will include confidential data where your identity will be kept anonymous which will describe and record your entire course from your admission to your discharge from the outpatient clinics one year later. The documentation will also include details from your medical history in order to have a complete medical profile of each patient enrolled at the study. None of these procedures or the duration of your follow-up are different from the standard clinical practice for these types of injuries.

Your GP will be also informed about your participation to the current clinical trial with a letter and also with a copy of the Patient Information Sheet you are currently reading.

6) DOES THIS STUDY INVOLVE ADDITIONAL PROCEDURES, APPOINTMENTS, OR INTERVENTIONS?

None of these procedures, or the duration of your follow-up are different from the standard clinical practice for these types of injuries. The average fracture healing period for these fractures is 4 to 6 months. The follow up at the outpatient fracture clinics of all the patients with such a fracture is continued for at least one year. As you can imagine the follow up

appointments may range to their frequency but as an average they are planned after 4 weeks 3 months 6 months 9 months and 12 months after the operation. These are exactly the scheduled appointments that you will also have according to the study protocol. The operation will be performed again exactly as we are currently treating these fractures and no additional steps or procedures will be undertaken for the study purposes. The investigations – plain radiographs and clinical examination that we will use for the study purposes, are again the usual means we use in daily orthopaedic trauma practice.

7) WHAT ARE THE PHASES OF THIS STUDY

In this study, there will be 2 equal groups of patients with **20** patients enrolled in each one.

Group A: POLYAX plate group (the locking plate of the company DePuy – Polyaxial Locked Plating System will be used at the time of surgery by a senior consultant orthopaedic surgeon).

Group B: LISS plate group (the locking plate of the company Synthes – Less Invasive Stabilization System will be used at the time of surgery by a senior consultant orthopaedic surgeon).

You will be randomly (by chance) assigned to one of the two treatment groups. You have an equal chance of being in any of the study groups. Your study doctor has no influence of the treatment group you are assigned to. This is done in order to obtain results as objective as possible.

Before you sign the consent form for this study, the study doctor or other eligible staff will explain the study to you. You will then be asked to read carefully and sign this consent form before the study doctor or staff can begin any of the screening procedures, which are done, in order to decide whether you are suitable for the study.

To be eligible for study participation, you must meet all of the following criteria:

i. You are willing and able to understand, sign and date the study-specific; Institutional Review Board/Ethics Committee approved patient informed consent and applicable privacy regulations.

ii. You must require surgical treatment of a periprosthetic fracture adjacent to components of a total knee arthroplasty, or of an osteoporotic distal femoral fracture.

iii. You are skeletally mature (≥18 years of age or radiographic evidence of closure of epiphyses).

iv. You were able to ambulate satisfactorily prior to the fracture incident.

v. You agree to participate in the post-operative clinical evaluations.

To be eligible for study participation, you must not meet any of the following criteria:

i. You have a clinically significant organic disease, including cardiovascular, hepatic, pulmonary, neurologic, or renal disease, or established dementia or other medical condition, serious intercurrent illness, or extenuating circumstance that, in the opinion of the Investigators, would preclude participation in the trial or potentially decrease survival or interfere with ambulation or rehabilitation.

ii. Your fracture is the result of an infection.

iii. You have a known metabolic bone disease or other condition (other than osteoporosis), which would negatively impact on the bone healing process (e.g. history of Paget's disease or other osteodystrophy).

iv. You are currently being treated with radiation, chemotherapy, immunosuppression, or chronic steroid therapy (prednisone use up to 5 mg/qd or its equivalent is allowed).

v. You have other fractures that would interfere with ambulation or rehabilitation.

vi. You have a condition, which places him/her at risk for osteomyelitis.

vii. You have an American Society of Anaesthesiologists (ASA) Physical Status Classification greater than 3.

viii. You have a life expectancy less than 24 months.

ix. Your fracture is an open fracture.

x. Your fracture is accompanied with a loosening of the original prosthesis, as this is determined preoperatively or intraoperatively (intraoperative exclusion criteria).

Once you have signed the written consent form, you will be allocated to the next available investigational subject number. This number will then become the unique identifier of yours and will be repeated at all documents and data. Together with your gender and date of birth, this number that represent you as far as the study will be concerned. In this way your anonymity will be kept safe.

INVESTIGATIONAL PROCEDURES

i) At the Screening Visit = your first study visit:

This visit will take place when you are in hospital and the doctor has identified you as having a fracture to your distal femur and that you have either evidence of osteoporosis (according to your medical history, or a specific radiologic index), or the fracture of yours is adjacent to the femoral component of a previous total knee arthroplasty implant, or both.)

This visit will assess whether you are suitable for taking part in the study. The following assessments will be done at this visit:

• A complete medical history, including any medications you take, concurrent diseases and previous fractures of any site.

• Demographic data e.g. race, ethnicity, date of birth, nicotine consumption, alcohol consumption, body weight and height

• Routine physical examination, including collection of your blood pressure, respiratory rate, pulse rate and body temperature.

• Routine Blood samples will be taken for routine preoperative safety assessment as in all similar fractures.

• Routine X-rays of your injured limb will be taken for routine preoperative assessment as in all similar fractures (if you have not had on your admission)

• You will need to complete 5 questionnaires (OKS, Weight bearing status, EuroQol, VAS) referring to the function of your injured knee and on your quality of life and health prior to your injury.

ii) Surgery (day 0 – all future appointments and dates will have this date as a starting referral)

After the Randomisation process (the computerised decision on the specific implant – plate to be used – based on chance) you will be operated with the standard techniques and well established methods of internal fixation, by an experience consultant surgeon with either of the plating systems (POLYAX or LISS), and any other necessary means needed for the best possible result.

You will receive general or spinal anesthesia and prophylactic treatments (to reduce the possibility of infection and of a blood clot) as per your usual routine care.

iii) On the day of your Discharge

The following assessments will be done at this visit:

• A review of any adverse events and medications you have taken.

• A review of your smoking status.

• You will need to complete the same 5 questionnaires (OKS, Weight bearing status, EuroQol, VAS) referring on your current quality of life and health and the function of your operated limb.

iv) 1st Follow-up appointment (4 weeks ± 7 days post-Surgery)

The following assessments will be done at this visit:

• X-ray examination of your distal femur with standard AP and lateral X-Rays, as is also the routine practice for all operated distal femoral fractures.

• A review of any adverse events and medications you have taken.

• A review of your smoking status.

• You will need to complete the same 5 questionnaires (OKS, Weight bearing status, EuroQol, VAS) referring on your current quality of life and health and the function of your operated limb.

v) 2nd Follow-up appointment (3 months ± 14 days post-Surgery)

The following assessments will be done at this visit:

• X-ray examination of your distal femur with standard AP and lateral X-Rays, as is also the routine practice for all operated distal femoral fractures.

• A review of any adverse events and medications you have taken.

• A review of your smoking status.

• You will need to complete the same 5 questionnaires (OKS, Weight bearing status, EuroQol, VAS) referring on your current quality of life and health and the function of your operated limb.

vi) 3rd Follow-up appointment (6 months ± 30 days post-Surgery)

The following assessments will be done at this visit:

• CT-scan examination of your distal femur that is the gold standard method of accurate diagnosis of bone healing around the knee joint – used routinely in clinical practice for this reason.

X-ray examination of your distal femur with standard AP and lateral X-Rays, as is also the routine practice for all operated distal femoral fractures.

• A review of any adverse events and medications you have taken.

• A review of your smoking status.

• You will need to complete the same 5 questionnaires (OKS, Weight bearing status, EuroQol, VAS) referring on your current quality of life and health and the function of your operated limb.

vii) 4th Follow-up appointment (9 months ± 60 days post-Surgery)

The following assessments will be done at this visit:

• X-ray examination of your distal femur with standard AP and lateral X-Rays, as is also the routine practice for all operated distal femoral fractures.

• A review of any adverse events and medications you have taken.

• A review of your smoking status.

• You will need to complete the same 5 questionnaires (OKS, Weight bearing status, EuroQol, VAS) referring on your current quality of life and health and the function of your operated limb.

viii) 5th Follow-up appointment (12 months ± 60 days post-Surgery)

The following assessments will be done at this visit:

• X-ray examination of your distal femur with standard AP and lateral X-Rays, as is also the routine practice for all operated distal femoral fractures.

• A review of any adverse events and medications you have taken.

• A review of your smoking status.

• You will need to complete the same 5 questionnaires (OKS, Weight bearing status, EuroQol, VAS) referring on your current quality of life and health and the function of your operated limb.

• If there is any query regarding the completion for the fracture healing a CT scan will be used to establish an accurate diagnosis, which is the gold standard method of accurate diagnosis of bone healing around the knee joint – used routinely in clinical practice for this reason.

In total you will be followed up for 1 year after your operation according to the study's protocol. If any additional follow-up is required additional to the 1st

year you will be followed up for as long as needed for your safe and full recovery.

The number of the necessary follow-up appointments does not surpass the actual number of appointments for postoperative assessment of similar fractures in routine clinical practice. Moreover the investigational and imaging methods to be utilised are also routine x-rays and CT-scans routinely used in daily clinical practice. No additional to the standard appointments or investigations will be employed for the purposes of this study.

6) WHAT DO I HAVE TO DO?

As a study participant, you are obliged to

• Follow the medical instructions by the study doctor and to adhere to the visit schedule.

• Accurately inform your study doctor about your progress and any undesired effects observed.

• Inform your study doctor about any changes that are made to your medication prescribed by a doctor and those you have bought yourself without a medical prescription.

7) WHAT ARE THE ALTERNATIVES FOR TREATMENT?

For the treatment of distal femoral osteoporotic or adjacent to a total knee arthroplasty fractures, the therapeutic options include:

- Non-operative treatment (bed rest – traction – brace for a period of several months);
- Intramedullary nailing (limited indications in the presence of severe osteoporosis, very distal fractures, or certain femoral components of total knee arthroplasties – with closed “box);

- Open reduction and plate fixation with plates of an older design and materials (DCS, Blade plate)
- External ring fixation (limited indications in the presence of severe osteoporosis, or the presence of adjacent total knee arthroplasty – danger of septic arthritis).

8) WHAT ARE THE POSSIBLE DISADVANTAGES AND RISKS OF TAKING PART?

Your health and safety are the most important considerations to the doctors performing this study. Your doctor and his colleagues will take care of you during the study and will take you out of the study at any time they feel your health is being affected.

All diagnostic and therapeutic procedures, interventions and investigations that will be used for the purposed of this study are all routine clinical and surgical practice of the department of trauma and orthopaedics where you are admitted. Both plating systems are used here and to most of the "modernized" world for a number of years with very good therapeutic results in these kind of fractures like yours (bone healing rates of 85%). Furthermore they are considered to be safe surgical procedures, and are mostly used with minimal surgical incisions and surgical insult to the fracture site.

You will benefit by the standard insurance coverage of the NHS patients, as NHS indemnity scheme will apply to all protocol authors.

9) WHAT ARE THE POSSIBLE BENEFITS FOR TAKING PART?

During their 1year of your follow-up you will benefit by the close follow-up of their recovery by the same team of physicians and the full documentation of their postoperative course.

Furthermore in order to minimize any undesired variables affecting the final outcome the operation will be performed definitely by an experienced consultant trauma surgeon, familiar with the use of these locking plates and with the operative treatment of difficult periprosthetic or osteoporotic fractures.

Another potential benefit to the research participants is that they will have the experience of a close relationship with the treating physicians and the study related medical and non-medical staff. They will be at the center of a large scientific effort to provide strong scientific evidence on the optimal fixation method and overall treatment of these most demanding injuries, and hopefully contribute on the evolution of the scientific knowledge.

10) WHAT HAPPENS WHEN THE RESEARCH STUDY STOPS?

It is anticipated that the entire study will take approximately 24 months to complete. Each patient treated by either of the internal fixation methods will participate in the study for 12 months (including baseline, randomisation, treatment and follow-up).

If the Sponsor, the Investigation site, the ethics committee or any other of the regulatory authorities decide that the study must be stopped early you will promptly informed and also be given the reason for this happening.

Your follow-up and further treatment will not be affected by such a happening as your treating doctor will be responsible for your whole course until recovery and discharge from the outpatient orthopaedics clinics, as also is the routine clinical practice.

11) WHAT IF THERE IS A PROBLEM?

Any compliant about the way you have been dealt with during the study or any possible harm you might suffer will be addressed. The detailed information on this is given in Part 2.

12) WILL MY TAKING PART IN THE STUDY BE KEPT CONFIDENTIAL?

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

Contact details:

If you have any questions whilst taking part in the study you should contact the following clinicians:

Prof. PV Giannoudis BSc, MB, MD, EEC(ortho)

Academic Dept. of Trauma & Orthopaedics

Leeds General Infirmary, Clarendon Wing, Level A, Great George Street, LS13EX, Leeds, UK.

Tel: 0113 392 2750

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Mr Nik K Kanakaris MD, PhD

Academic Dept of Trauma and Orthopaedics

Leeds General Infirmary, Clarendon Wing, Level A, Great George Street, LS13EX, Leeds, UK.

Tel: 0113 392 2750

Fax: 0113 392 3290

Or via the Switchboard of the Leeds General Infirmary

(0113 243 2799)

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.

WHAT IF RELEVANT NEW INFORMATION BECOMES AVAILABLE?

Sometimes during the course of a research project, new information becomes available about the treatment that is being studied. If this happens, your study doctor will tell you about it and discuss whether you want to or should continue in the study.

If you decide not to carry on, your study doctor 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.

Also on receiving new information your study doctor might consider it to be in your best interest to withdraw you from the study. He/She 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.

WHAT WILL HAPPEN IF I DON'T WANT TO CARRY ON?

Your participation in this clinical study is completely voluntary. You may refuse to participate for any reason. If you choose to participate, you may discontinue your participation at any time and for any reason without penalty or loss of benefits.

If you decide not to participate in this clinical study, your doctor will continue to provide you with medical care. If you decide that you do not want to attend the follow-up visits, then your doctor may arrange different follow-up visit as part of the routine care. In these circumstances, unless you object, the follow-up information will also be used for the purposes of the study. You will not have to give reasons for withdrawing your consent or for discontinuing the clinical study.

WHAT IF THERE IS A PROBLEM?

In case of uncertainties, emergencies, and unexpected or undesired events occurring during or after the clinical study, you may contact the following person at any time:

Name: Mr Nik K. Kanakaris MD PhD

Address: Academic Dept of Trauma and Orthopaedics, Leeds General Infirmary, Clarendon Wing, Level A, Great George Street, LS13EX, Leeds, UK

Mobile Tel: 0788 789 77 25

If you have a concern about any aspect of the study, you should speak with the study doctors who will try their best to answer your questions. 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.

WILL MY TAKING PART IN THIS STUDY BE KEPT CONFIDENTIAL?

If you join the study, some parts of your medical records and the data collected for only authorized persons will look at the study from the company sponsoring and/or the company organizing the research. They may also be looked at by representatives of the local authorities and by authorized people from the trust to check that the study is being carried out correctly. All will have a duty of confidentiality to you as a research participant and nothing that could reveal your identity will be disclosed outside the research site.

All personal data obtained (including your state of health and demographic details will be electronically stored in coded form (identified only by number, initials and/ or date of birth) and further processed in strict compliance with applicable data protection laws under the control of the

sponsor for scientific, regulatory and future medical or pharmaceutical research purposes.

All your records will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. Your identity will remain confidential, even in the case the results of the study are published.

Only the hospital will have access to the code-keys, by which your identity can be linked to the patient number, initials and/or date of birth. Your samples will be stored in coded form for a period of five years or longer if required by mandatory law, and thereafter destroyed.

In the event of withdrawal of your consent to participate in the study, no new personal data pertaining to your participation in the study will be collected. If you wish no further use of your personal data that have already been collected, you need to state that explicitly.

You have certain statutory rights, which allow you to have access to and to require corrections of your personal data. Such queries should be directed to the sponsor. Your General Practitioner will be informed of your participation in this study and you should be aware that by signing consent to take part in the study, you are agreeing to this.

WHAT WILL HAPPEN TO THE RESULTS OF THE RESEARCH STUDY?

The data and results from this survey may be published in medical journals or used in scientific reports, but your name will never appear. You will be able to obtain copies of any such published reports from your doctor.

WHO IS ORGANISING AND FUNDING THE RESEARCH?

The company organising and funding this research is DePuy, Warsaw, Indiana; USA.The Primary Site of Investigation (SI) will be the

Academic Department of Trauma and Orthopaedics, Leeds Teaching Hospitals, School of Medicine, University of Leeds. The Primary Investigator (PI) will be the head of the later, Professor Peter V. Giannoudis.

WHO HAS REVIEWED THE STUDY?

An independent research ethics committee reviews all proposals for research using human subjects before they can proceed. This study was given favorable ethical opinion for conduct in the NHS by the Northern and Yorkshire Research Ethics Committee.

Thank you for considering to take part and taking the time to read this. You will be given a copy of the Information sheet and the informed

NHS

UNIVERSITY OF LEEDS

PATIENT CONSENT FORM

Subject ID No: | | | - | | | | **Patient Initials:** | | |

A Randomised Controlled Pilot Trial of Two Locking Plate Fixation Systems for Periprosthetic or Osteoporotic Distal Femoral Fractures: PolyAx vs. LISS

	Please initial box
1. I confirm that I have read and understood the Information Sheet for the above study. I have been given time and opportunity to ask questions about the study and all my questions were answered to my satisfaction. I have been given a copy of the Information Sheet and Consent Form to keep.	☐
2. 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.	☐
3. I understand that sections of my medical notes may be looked at by responsible individuals of the Investigational site, the Ethics Committee or Regulatory Authorities where it is relevant to my taking part in this study. I give permission for these individuals to have access to my records.	☐
4. I am aware that my personal data will be collected and processed by Leeds General Infirmary as a result of my participation in this study. As required by the Data Protection legislation, I have received information on the purpose for the collection and processing of this data and on who will have access to the data and on my rights to access and correct the data. I give permission for this data collection, processing and transfer of my data.	☐
5. I agree to the transfer of personal data to Leeds General Infirmary in the Economic European Union (EEU).	☐
6. I agree that my Family Doctor may be advised of my participation in this study.	☐
7. I agree to take part in this study.	☐

Name of Subject	Date	Signature
Name of Person taking consent (if different from surgeon)	Date	Signature
Surgeon	Date	Signature