

MAIN TITLE

Knee Fix Or Replace Trial (KFORT)

SUBTITLE

A Randomised Controlled Feasibility Study

ABSTRACT

Aims:

To assess the feasibility of conducting a full-scale, appropriately powered, randomised controlled trial (RCT) between internal fracture fixation and distal femoral replacement (DFR) for distal femoral fractures in older people.

Patients and Methods:

A total of 7 centres recruited patients to the study. Patients were eligible if aged 65 and over with a distal femoral fracture and the surgeon felt they were suitable for either treatment. Feasibility outcome measures included patients willingness to participate, clinicians willingness to recruit, dropout rates, ability to capture data, estimates of standard deviation to inform the sample size calculation and the main cost-drivers. The primary clinical outcome measure was EQ-5D at 6-months following injury.

Results

Of the 36 patients who met the inclusion criteria, 5 declined to participate and 8 were not recruited, leaving 23-patients to randomise. 1 patient withdrew before surgery, 5/22 (23%) withdrew during the follow-up period and 6 (26%) patients died. A 100% response rate was achieved for the EQ-5D at each follow-up point, aside from one missing data point at baseline. For the DFR group, the mean implant cost outweighed the mean cost for many other items, including theatre time, length of stay and re-admissions. For a powered trial, a total sample size of 1400 would be required; hence requiring 234 centres, recruiting over 3 years. At 6-months, the EQ-5D utility index was lower in the DFR group.

Conclusion

This study has found running a full-scale trial in this country not feasible. However, it

may be feasible to perform an international multi-centre trial and this study provides some guidance in terms of powering a study, the numbers required and some challenges to anticipate and address.

INTRODUCTION

Fractures of the distal femur occur in a bimodal age distribution. In younger patients, they are typically as a result of high-energy trauma, however, in older patients they are commonly lower energy injuries. There are 5-7000 distal femur fractures in older patients occurring in the United Kingdom (UK) each year ¹. This is a vulnerable patient group; pre-existing medical co-morbidities are common ²⁻⁵ and a recent study of older patients with similar fractures found that approximately 30% have cognitive impairment ⁶. Furthermore, these patients often have osteoporosis and fragile, poor soft tissues which can create further difficulties when managing these injuries ⁷.

Distal femoral fractures are commonly treated operatively with internal fracture fixation, using either a plate and screws, or an intramedullary nail ⁸. This has the benefit of preserving the patient's own bone, but has approximately a 20% risk of non-union; ⁷ often patients are restricted in their post-operative weight-bearing status, hence requiring prolonged institutional care ⁴. Cost implications therefore are not only limited to the surgical intervention and implant used, but a lot of the cost can be attributed to the patients' post-operative rehabilitation and length of institutional stay. A summary of the evidence from the Cochrane collaboration⁶ concluded that the evidence available for the management of distal femoral fractures in the older patient remains inconclusive and insufficient to inform current clinical practice ⁹.

Furthermore, a recent study looking at the treatment of older patients sustaining distal femoral fractures highlighted a disparity and lack of consensus in their management when compared with neck of femur fractures in a similar patient cohort. The principles of early surgery to allow full weight bearing and universal orthogeriatric involvement have not been extended to the distal femur patient cohort⁴.

An alternative treatment option for these fractures in older patients is a distal femoral replacement (DFR). This has been suggested to be beneficial, in small case series,

as it allows immediate post-operative full weight-bearing, negates the risk of non-union and may provide greater patient satisfaction scores^{10,11}. However, DFR has its own potential risk profile, most notably deep prosthetic joint infection and implant loosening. Whilst a DFR is a more costly implant as compared to fracture fixation devices, the initial increased cost, may be offset by quicker rehabilitation and return to usual place of residence ¹¹.

In this randomised controlled, multicenter, prospective feasibility study, Knee Fix or Replace Trial (KFORT) we compared internal fracture fixation with DFR for older patients sustaining a distal femoral fracture. The primary objective of this study was to assess the feasibility of performing a full-scale prospective randomised trial. The secondary objective was to compare clinical outcome measures between internal fracture fixation and DFR for distal femoral fractures in the older population.

PATIENTS AND METHODS

A total of 9-centres in the UK agreed to participate in this trial, out of which 7-centres recruited patients to the study. These included major trauma centres or trauma units with the appropriate trauma and arthroplasty expertise to perform the two procedures. Study participants were recruited if they were over 65-years of age, had a distal femoral fracture and the treating surgeon felt they were potentially suitable for either internal fracture fixation or DFR. Patients were excluded from the trial if they had an ipsilateral knee replacement, the fracture was open, the patient was unfit for anaesthesia, or the patient was immobile prior to the injury. Patients with cognitive impairment were not excluded from the study, but in accordance with the Mental Capacity Act 2005, agreement to participate was taken from an appropriate consultee. Patients' demographics, comorbidities and pre-injury functional status were recorded after consent was given by the participants or obtained by proxy. The randomisation sequence was generated by the Cambridge Clinical Trials Unit through a secure web-based randomisation service. Randomisation was on a 1:1 basis, with minimisation by intra-articular extension of the fracture and the patient's cognitive state. Minimisation by intra-articular extension eliminated a potential confounder, as disruption of the articular surface can predispose to secondary arthritis of the knee. We also minimised on the basis of cognitive impairment, as we felt this may have a substantial bearing on the outcome.

In the internal fracture fixation group, patients were treated with either a lateral locking plate, or a locked retrograde femoral nail, as per treating surgeon's preference. The only stipulation was that if a plate was used, the screws in the distal portion of the bone were locked into the plate. The DFR group, were treated with a DFR using standard surgical techniques with a prosthesis chosen by the operating surgeon. This pragmatic study intentionally did not standardise a type or brand of implant for either of the two options. Following surgery, the patients were

rehabilitated in the treating consultant's usual manner. The details of this rehabilitation programme were recorded and included their weight-bearing status after surgery and the frequency of physiotherapy contacts. The study is registered within the ISRCTN registry (ISRCTN16109266).

Outcome measures

Feasibility for a full-scale trial was assessed by the willingness of patients to participate and clinicians to recruit, drop-out rates, the ability to capture all data, estimates of standard deviation to inform the sample size calculation for the full trial, completion rates and the main cost-drivers, to inform the decision as to how costs and benefits should be measured in a definitive trial. Costs were estimated over the 9 month follow-up period from the perspective of the NHS and Personal Social Services (PSS) ¹² based on 2016/2017 financial year price levels and no discounting was undertaken. Sites were asked to record equipment used in relation to each study treatment, along with theatre time, original length of stay, and any additional procedures or hospital re-admissions (these costs were summed to estimate total hospital costs). At 6-weeks, 6-months and 9-months post randomisation, participants who had been discharged from hospital (and were not deceased) were asked about other NHS and PSS items of resource-use, including discharge destination e.g. care/nursing home (all associated costs were assumed to be incurred by NHS and PSS, for the reported time period), and details of any additional equipment e.g. zimmer frame or health professional visits (costs for items reported as paid for by participants were excluded from the analysis). Mean costs were estimated, with available data on each item of resource use, total costs (over the 9-month follow-up period) are based on participants who had data available for all component costs.

The primary clinical outcome measure was EQ-5D at 6-months following injury. The

EQ-5D provides a health description based on five dimensions and the 5 level version was used (EQ-5D-5L)¹³. The EQ-5D health status instrument was chosen as it is the outcome of most importance to patients in the UK Hip Fracture Core Outcome Set, is validated for completion by proxy in patients with cognitive impairment and for use in older patients sustaining other lower limb fractures¹⁴. It was collected by proxy if the patient lacked capacity to consent on admission. The primary outcome time was chosen to be at 6-months after injury, as recovery in quality of life appears to plateau in the first few months after analogous injuries in a similar population¹⁵ and there would not be too great a loss of patients to death. As recommended by the National Institute of Clinical Excellence (NICE)¹⁶, EQ-5D responses were converted to health state utility values using the cross walk method¹⁷, and if death occurred during the study patients were assigned a score of 0 (a score of 1 is equivalent to full health)¹⁸. The secondary outcome measures included the Oxford Knee Score (OKS) and the Disability Rating Index (DRI). Both the OKS (0-48, where 48 represents best function) and DRI (0-100, where 100 denotes complete disability) are self-administered patient questionnaires, assessing symptoms and disability related to the lower limb^{19 20}. These scores were only collected for patients without cognitive impairment, as they are not validated for collection by proxy. The EQ-5D and secondary outcome measures were completed in person at baseline, 6-weeks and 9-months and by post or telephone at 6-months. Complications were collected and grouped as either intra-operative or post-operative.

Sample size and statistical analysis

As this was a feasibility trial, no sample size calculation was performed. The aim was to collect primary clinical outcome data on a minimum of 24 patients (12 in each arm) to inform a sample size calculation for a full-scale randomised trial based on the work of Julious²¹. Therefore, a target recruitment of 46-patients was set, which, allowing for 20% loss to follow-up and 20% mortality at 6-months, would generate 6-month

follow up data for 29-patients (at least 14 in each arm). The analysis was performed on an intention-to-treat basis and included all eligible patients that received any study treatment and had at least one post-baseline assessment. A pooled estimate of the standard deviation of the primary outcome was calculated in order to inform the sample size required for a full-scale trial. Forest plots of the EQ-5D utility index by treatment and time were produced. Due to small numbers of patients completing the DRI and OKS, scatterplots of these outcomes by treatment and time were produced. Pre-planned exploratory analyses of the EQ-5D, DRI, and OKS by age (below 80-years, above 80-years) and fracture type (extra-articular/intra-articular) were undertaken in a similar manner. For the EQ-5D outcomes, exploratory analysis by capacity status (with/without) was also undertaken. All statistical analysis was carried out with the software R, The R Project for Statistical Computing, R Foundation for Statistical Computing, Vienna, Austria.

RESULTS

From 23 October 2015 to 15 August 2017, 36 patients were found to be eligible for the trial (figure 1). Of these patients, five declined to participate and eight were not randomised as the research team were unavailable, leaving 23 patients to randomise. Patients were excluded from the study if the surgeon felt very strongly that either internal fracture fixation or DFR was more appropriate for the patient. There were no patients who were excluded from the trial due to this reason. One of the patients randomised to internal fracture fixation received a DFR as it was felt, intra-operatively, “fixation was not appropriate due to presence of severe arthritis in the knee and poor bone quality with comminution”. This internal fracture fixation participant was included in all analyses, as randomised, in line with the intention to treat principle. All patients randomised to DFR received the treatment as allocated. One patient in the internal fracture fixation group withdrew consent for involvement in the trial before surgery and hence could not be included in data analysis, leaving a full analysis population of 11 in each group. Seven patients in the internal fracture fixation group and 7 patients in the DFR group completed their 6-month follow-up questionnaires. All included patients were female. Further details on the patients’ characteristics are presented in table 1.

Feasibility Outcomes

Of the 36 eligible patients, only five declined to participate in the trial, while the clinicians were happy to recruit all eligible patients to the trial. 1 patient withdrew before surgery and 5 of the remaining 22 (23%) patients recruited to the trial withdrew after the surgical procedure for various reasons. During the follow-up period, six (26%) patients died. At each follow-up point, a 100% response rate was received from all participants who were asked to complete the EQ-5D questionnaire. However, EQ-5D data was missing for one participant at baseline. Lower rates of completion of the secondary outcome measures were noted, as patients without

mental capacity were unable to complete these measures. The estimated pooled standard deviation was 0.382 for the EQ5D. Response rates for the different cost components are shown in Table 2a, where it can be seen that very few items of data were missing (the lowest response rate for any individual variable was 77% after taking into account deaths and withdrawals). Table 2b shows the mean level of resource costs incurred for the two groups.

Clinical Outcomes

Figure 2 shows the mean EQ-5D scores at all time-points, along with 95% confidence intervals. The OKS and DRI could only be collected in patients who had mental capacity (Tables 3&4). Blood transfusion rates for each group were very similar. All patients, in both groups, were instructed by the treating surgeon to be fully weight bearing, or weight-bearing as tolerated. 22% of those in the DFR group and 50% of those in the ORIF group were walking with or without aids prior to discharge. Figure 3 shows that patients in both groups lost independence of living after the injury. 73% of patients in each group were living independently or in sheltered-accommodation pre-injury. There were no intra-operative complications in either group. Post-operative complications directly related to the procedure included one late stress fracture occurring between the stem of the DFR and the stem of a pre-existing hip replacement; this was treated with plate fixation. There was one wound complication in the DFR group, which resolved with antibiotics requiring no surgical intervention. One patient in the internal fracture fixation group had a diagnosis of compartment syndrome recorded. There was one diagnosis of non-fatal post-operative pulmonary embolism in the DFR group.

DISCUSSION

Our primary objective was to evaluate the potential for undertaking a full-scale, appropriately powered, prospective RCT. Whilst all clinicians in our study-centres were happy to recruit all eligible patients, of the 36 eligible patients, 5 declined to participate. We did note, however, that the youngest patient recruited was 77, suggesting that clinicians may have felt that patients younger than this were not eligible for a DFR, and hence the trial. It was also noted that 18 of the 23 recruited could only walk 400m or less pre-injury. During the follow up period, 5/21 (24%) patients withdrew from the trial and 6/21 (29%) patients died. Despite overall small numbers, these withdrawal rates were felt to be high, however, the death rate was as expected in this patient population. All remaining patients completed the primary outcome measure (EQ-5D) at 6 months. Much poorer rates of completion of the secondary outcome measures were noted, mainly due to the fact that they could not be completed if the patient lacked capacity. The estimated pooled standard deviation for the EQ-5D was 0.382. To run a full scale powered trial, we would require a total sample size of 1400 for an optimistic minimal clinically important difference (MCID) of 0.074 for the EQ-5D, with a power of 0.9, and loss to follow-up of 20% ²². Over the period of this trial, 23 patients were recruited from 9 participating centres. This equates to less than 2 recruits per centre per year which was fewer than expected. Recruitment rate was one of the pre-specified feasibility criteria and therefore the low recruitment rate is a key finding of the study. Therefore, to run a full-scale trial over 3 years, one would require approximately 234 centres, recruiting 2 patients per year. In England there are 168 acute care trusts many of which operate hospitals on more than one site ²³. Nevertheless, it is clear that a full-scale trial would not be possible in England alone.

After taking account of deaths and withdrawals, a very high completion rate was achieved for both cost and benefit (EQ-5D) data. DFR implant costs were a large

cost-driver, though these participants also have other considerable costs (mean theatre time was about 2 hours, mean length of stay was > 20 days and 8 patients stayed in a care home at some point after discharge from hospital). Estimated costs are also presented in Table 2b. For the DFR group it can be seen that the implant cost outweighs that for many other items, including theatre time, length of stay and re-admissions, and explained much of the difference in overall costs between groups. Though other NHS and PSS costs post-discharge were also high, there is again a particular need to treat these results with caution, due to small numbers. Missing resource use data for any item would have meant this variable was not complete, and no data for that participant would thereby have contributed to the total cost estimates.

There is limited evidence in the literature on the treatment of distal femoral fractures in the older population, with no RCT's and only relatively small case series. This is the first RCT attempting to address this specific question. Bettin et al, wrote-up a case series of 18 older patients who had sustained a distal femoral fracture, and concluded that DFR "is a viable treatment option in older patients that permits immediate full weight-bearing, with most patients returning to preoperative functional status" ¹¹. Whilst both groups in our study were encouraged to mobilise fully weight-bearing immediately after surgery, only 22% of those in the DFR group and 50% of those in the internal fracture fixation group were walking on discharge. Furthermore, our data showed that in fact more patients had returned to independent living in the internal fracture fixation group than the DFR group. Though a 100% response rate was achieved for the EQ-5D questionnaire at each follow-up point, the small sample size (n=18 at 6-weeks, n=14 at 6-months and n=12 at 9-months) means that conclusions about trends or differences between groups cannot be drawn. Similarly, we are unable to comment on differences in patients' clinical outcome scores or quality of life scores, as this feasibility trial was not statistically designed to provide a

definitive answer with regards to the best method of treatment for distal femoral fractures in older patients.

In a retrospective review of 38 patients sustaining AO-33C, distal femoral fractures (i.e. intra-articular fractures) it was found that around 1 in 5 patients developed a non-union after ORIF and at 1-year follow-up, all patients in the DFR group were ambulatory, while 1 in 4 in the ORIF group were wheelchair bound ²⁴. Moloney et al. also found that out of 126 patients who were still alive at 1-year, 24% had developed a non-union⁷. Therefore, it was considered that a DFR, although, initially more costly, may reduce overall societal costs, as patients may be able to rehabilitate faster. However, from our study, we found a similar length of acute hospital stay, and in fact less return to usual place of residence in the DFR group (this explains the higher non hospital costs in Table 2b). We found the costs in the DFR group to be higher than the internal fracture fixation group in terms of implant costs, and this largely explained any differences in overall hospital costs. We also found more complications in the DFR group which may reflect the complexity of this surgery in a frail older patient group. However, as this is a feasibility study with small numbers, we have been unable to conclude a clinically significant difference. Our study found a combined mortality rate of 26% by 9-months post-injury. This rate is similar to a retrospective review of 176 patients over the age of 60, in which Moloney et al. found that 25% had deceased at 1-year ⁷. Drawing conclusions from comparative mortality rates between our two groups would be inappropriate; due to the small numbers and we feel it would be incorrect to retrospectively analyse data that did not form part of the initial statistical analysis plan.

Limitations

This RCT included patients with cognitive impairment, is multi-centre, and used validated patient reported outcome measures, as well as performing a detailed health economic evaluation. It's pragmatic nature, although also a strength, does expose such a trial to surgeon bias. A lack of surgeon equipoise could potentially result in patients being withheld from study participation due to the surgeons' opinion of the two treatment options. When beliefs regarding the effectiveness of an intervention exist, randomised trials could selectively recruit participants with a lower possibility of benefit, thereby diminishing the applicability of trial results to routine practice.

Patients were recruited if the surgeon deemed the fracture pattern and the patient were suitable for a surgical procedure, whether for fixation or for DFR. With this type of study there is clearly the need to strike a balance between having very tight eligibility criteria, limiting external validity against a more pragmatic approach providing information for a wider group.

However, this feasibility study was able to estimate a pooled standard deviation and determine a MCID value in our primary clinical outcome measure (EQ5D) on which to determine the sample size required for a full-scale randomised trial. Furthermore, EQ5D is the outcome measure selected by patients as the most important to them and so other outcome measures, including death, would not be suitable for a full-scale trial. In fact, we suspect that a power calculation based upon a categorical outcome measure, like death, would actually need a much larger sample size.

CONCLUSION

This feasibility study has found, that in order to run a full-scale, powered trial to show a difference in clinical outcome between internal fracture fixation and DFR for distal femoral fractures in the older population, one would require a total sample size of 1400 patients, which over a 3-year period would require approximately 234 centres recruiting 2 patients per year. We feel that this would be unrealistic and therefore running a full-scale trial in the UK is not feasible, based on the numbers required to power it. However, it may be feasible to perform an international multi-centre trial and this study provides some guidance in terms of powering a study, the numbers required and some challenges to anticipate and address.

Conflict of interest statement

All authors declare that they have no conflict of interest.

Funding statement

This paper presents independent research funded by the NIHR under its Research for Patient Benefit (RfPB) Programme (Grant Reference Number PB-PG-1013-32019) and was supported by the National Institute for Health Research (NIHR) and the Oxford Biomedical Research Centre. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health. Aquilant provided excess treatment costs of the DFR implants for the purposes of the trial but had no part in the design, delivery or reporting of the trial.

REFERENCES

1. **Court-Brown CM, Caesar B.** Epidemiology of adult fractures: A review. *Injury* 2006;37-8:691-7.
2. **Streubel PN, Ricci WM, Wong A, Gardner MJ.** Mortality after distal femur fractures in elderly patients. *Clin Orthop Relat Res* 2011;469-4:1188-96.
3. **Bohm ER, Tufescu TV, Marsh JP.** The operative management of osteoporotic fractures of the knee: to fix or replace? *J Bone Joint Surg Br* 2012;94-9:1160-9.
4. **Smith JR, Halliday R, Aquilina AL, Morrison RJ, Yip GC, McArthur J, Hull P, Gray A, Kelly MB, Collaborative - Orthopaedic Trauma S.** Distal femoral fractures: The need to review the standard of care. *Injury* 2015;46-6:1084-8.
5. **Jennison T, Divekar M.** Geriatric distal femoral fractures: A retrospective study of 30 day mortality. *Injury* 2018.
6. **Griffin XL, Achten J, Parsons N, Costa ML.** Platelet-rich therapy in the treatment of patients with hip fractures: a single centre, parallel group, participant-blinded, randomised controlled trial. *BMJ Open* 2013;3-6.
7. **Moloney GB, Pan T, Van Eck CF, Patel D, Tarkin I.** Geriatric distal femur fracture: Are we underestimating the rate of local and systemic complications? *Injury* 2016;47-8:1732-6.
8. **Zlowodzki M, Bhandari M, Marek DJ, Cole PA, Kregor PJ.** Operative treatment of acute distal femur fractures: systematic review of 2 comparative studies and 45 case series (1989 to 2005). *J Orthop Trauma* 2006;20-5:366-71.
9. **Griffin XL, Parsons N, Zbaeda MM, McArthur J.** Interventions for treating fractures of the distal femur in adults. *Cochrane Database Syst Rev* 2015-8:CD010606.

- 10. Appleton P, Moran M, Houshian S, Robinson CM.** Distal femoral fractures treated by hinged total knee replacement in elderly patients. *J Bone Joint Surg Br* 2006;88-8:1065-70.
- 11. Bettin CC, Weinlein JC, Toy PC, Heck RK.** Distal Femoral Replacement for Acute Distal Femoral Fractures in Elderly Patients. *J Orthop Trauma* 2016;30-9:503-9.
- 12. (NICE) NifHaCE.** Guide to the methods of technology appraisal 2013. *NICE webiste* 2013.
- 13. Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, Bonsel G, Badia X.** Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res* 2011;20:1727-36.
- 14. Hounsime N, Orrell M, Edwards RT.** EQ-5D as a quality of life measure in people with dementia and their carers: evidence and key issues. *Value Health* 2011;14-2:390-9.
- 15. Griffin XL, Parsons N, Achten J, Fernandez M, Costa ML.** Recovery of health-related quality of life in a United Kingdom hip fracture population. The Warwick Hip Trauma Evaluation--a prospective cohort study. *Bone Joint J* 2015;97-B-3:372-82.
- 16. NICE.** Position statement on use of the EQ-5D-5L valuation set for England *NICE guidance webiste* 2018;*NICE Technology Appraisal Guidance*
- 17. van Hout B, Janssen MF, Feng YS, Kohlmann T, Busschbach J, Golicki D, Lloyd A, Scalone L, Kind P, Pickard AS.** Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. *Value Health* 2012;15-5:708-15.

- 18. Parsons N, Griffin XL, Achten J, Chesser TJ, Lamb SE, Costa ML.** Modelling and estimation of health-related quality of life after hip fracture: A re-analysis of data from a prospective cohort study. *Bone Joint Res* 2018;7-1:1-5.
- 19. Dawson J, Fitzpatrick R, Murray D, Carr A.** Questionnaire on the perceptions of patients about total knee replacement. *J Bone Joint Surg Br* 1998;80-1:63-9.
- 20. Salen BA, Spangfort EV, Nygren AL, Nordemar R.** The Disability Rating Index: an instrument for the assessment of disability in clinical settings. *J Clin Epidemiol* 1994;47-12:1423-35.
- 21. Julious SA.** Sample size of 12 per group rule of thumb for a pilot study. *Pharmaceutical Statistics* 2005;4-4:287-91.
- 22. Walters SJ, Brazier JE.** Comparison of the minimally important difference for two health state utility measures: EQ-5D and SF-6D. *Qual Life Res* 2005;14-6:1523-32.
- 23. NHS Trusts**
<https://www.nhs.uk/servicedirectories/pages/nhstrustlisting.aspx>. 2019.
- 24. Hart GP, Kneisl JS, Springer BD, Patt JC, Karunakar MA.** Open Reduction vs Distal Femoral Replacement Arthroplasty for Comminuted Distal Femur Fractures in the Patients 70 Years and Older. *J Arthroplasty* 2017;32-1:202-6.

Figure legends

Figure 1: CONSORT diagram

Figure 2: Plot of mean EQ-5D-5L utility index and 95% confidence intervals by treatment group and time.

Figure 3: Stacked bar chart showing residence prior to admission and at follow-up times by treatment group.