Abstract

Aim

To estimate the cost effectiveness of intramedullary nail fixation in comparison to 'locking' plate fixation for the treatment of extra-articular fractures of the distal tibia.

Methods

An economic evaluation, from the UK National Health Service (NHS) and personal social services (PSS) perspective, was conducted based on evidence from the Fixation of Distal Tibia Fractures (UK FixDT) multicentre, parallel trial. Data from 321 patients were available for analysis. Costs were collected prospectively over the 12-month follow-up period using trial case report forms and participant-completed questionnaires. Cost-effectiveness was reported in terms of incremental cost per quality adjusted life year (QALY) gained and net monetary-benefit. Sensitivity analyses were conducted to test robustness of the cost-effectiveness estimates.

Results

Mean NHS and PSS costs were significantly lower for patients treated with nail fixation over those treated with locking plate (-£970, 95% CI: -1685 to -256; P=0.05). There was a small increase in QALYs gained in the nail fixation group (0.01, 95% CI: -0.03 to 0.06; P=0.52). The probability of cost-effectiveness for nail fixation exceeded 90% at cost-effectiveness thresholds as low as £15,000 per additional QALY. The cost-effectiveness results remained robust to several sensitivity analyses.

Conclusions

This trial-based economic evaluation suggests that nail fixation is a cost-effective alternative to locking plate fixation.

Clinical Relevance of Paper

- The paper adds important evidence on the cost-effectiveness of alternative treatment options for extra-articular fractures of the distal tibia.

Introduction

Optimal management of extra-articular fractures of the distal tibia remains disputed. Although plates and intramedullary (IM) nails represent two viable approaches to internal fixation of these fractures, each possesses distinct disadvantages. The bolts or screws that are inserted into the nail may break, mal-alignment of the bone may occur, and there is an increased risk of anterior knee pain [1]. Whilst tibial plating with 'locking' plates can achieve accurate reduction, the need for greater soft tissue dissection increases the risk of infection, wound breakdown and damage to the surrounding structures [1, 2].

Evidence from previous meta-analyses and systematic reviews comparing nailing versus plating treatment modalities have been inconclusive. Mao *et al* reviewed 1863 extra-articular fractures of the distal tibia [3]. They reported that rates of deep infection, delayed union and removal of instrumentation were similar for patients undergoing nail and plate fixation, but nail fixation was associated with significantly more mal-unions. In contrast, Zelle *et al* found that mal-union rates were similar between the two treatment groups [4]. However, the studies included in the meta-analyses had heterogeneous study designs and the randomised controlled trials lacked methodologic rigour [3].

The prolonged recovery and rehabilitation following a distal tibia fracture, along with complications associated with treatment choice, have important economic consequences. These injuries not only generate direct treatment costs but indirect costs, including income losses due to work absences. Given rapidly escalating health care costs, and the need to allocate finite health care resources more efficiently, the costs associated with nail and locking plate fixation should be considered alongside the clinical benefits. Data comparing the clinical and cost-effectiveness of intramedullary nail and locking plate management of distal tibial fractures are currently limited. Available data are based on assessments of intramedullary nails alone [5], different plates for fixation alone [6], or compare nail fixation with interventions other than locking plates.

We present a prospectively-conducted health economic evaluation from a multi-centre randomised controlled trial of intramedullary nail fixation versus locking plate fixation for the treatment of adult patients with a displaced fracture of the distal tibia.

Patients and methods

Trial background

Data from the Fixation of Distal Tibia Fractures (UK FixDT) trial formed the basis of the economic evaluation [7]. Briefly, patients were eligible for the trial if: (i) they had a fracture that involved the distal tibial metaphysis; (ii) were aged 16 years or over; and (iii) the treating surgeon believed that they would benefit from internal fixation of the fracture. Participants were recruited from 28 UK Trauma Hospitals between April 2013 and February 2016 and followed-up for one year. They were randomly allocated to either intramedullary nail fixation or locking-plate fixation. All surgery was performed according to the preferred technique of the operating surgeon. A sample size of 320 was required to detect, with 90% power at the 5% level, a difference of 8 points in the primary clinical outcome, namely the disability rating index (DRI). Full details of the trial protocol are available in open access [1].

Ethics committee approval

The FixDT trial was approved by the Coventry and Warwickshire Research Ethics Committee on 06 November 2012 (REC reference: 12/WM/0340) and by the Research and Development department of each participating centre.

Study Perspective and Time Horizon

The primary analysis was undertaken from the perspective of the UK National Health Service (NHS) and Personal Social Services (PSS) as recommended by the National Institute of Health and Care Excellence (NICE) [8]. The time horizon for the economic evaluation followed the 12-month follow-up period of the trial, and therefore no discounting of costs and benefits was required. Under normal circumstances, uncomplicated fractures of the distal tibia would be expected to be clinically united at 6 months and patients returned to normal activities [2, 9]. The 12-month follow-up period is thus well suited to capture clinically important differences between the two procedures and in non-unions that result in revision fixations and rehospitalisation.

Measurement and valuation of resource use

Estimation of the costs associated with the interventions included the cost of the initial surgery and the broader health and PSS resource inputs, plus, for the purposes of a sensitivity analysis, personal costs and broader societal resource inputs. All costs were expressed in £ sterling and valued in 2014-15 prices. Where appropriate, costs were inflated or deflated to 2014-15 prices using the NHS Hospital and Community Health Services Pay and Prices Index [10].

Cost of distal tibia fixation

The initial surgical costs (intervention costs) were based on the initial hospital stay and associated operative costs as reported in table I. Unit costs were estimated using NHS reference costs, and the Healthcare Resource Groups (HRG) tariff for 'major knee procedures for trauma'[11]. Based on this tariff, distal tibia fixation costs the NHS £5315.47 if a patient stays in hospital an average of 5 days. Costs of the initial surgery were derived for each patient using the mean length of stay reported in the patient records. An excess bed day value of £327.00 was used to adjust the surgery costs of patients who stayed in hospital longer than 5 days. We assumed that treatment costs were disproportionately weighted towards the first 3 days of each initial hospital admission. Thus, the cost to the NHS of a patient who stayed in hospital for 3 days was calculated as £5315.47 – (2x£327), i.e. the 5-day tariff minus the bed day cost of £327 per each day not spent in hospital. The numbers of implants used during the surgery were derived from patient records. Unit costs for these implants were provided by the University Hospitals of Coventry and Warwickshire NHS trust finance department.

Broader resource use

Broader resource use over the 12-month follow-up period was captured via follow-up postal questionnaires, which were completed at 3-, 6- and 12-months post-randomisation. For the 3-month data, the recall period was since hospital discharge whilst at other time points, it was since completion of the previous questionnaire. The questionnaires captured the number, duration and type of hospital re-admissions following initial surgery, number and type of hospital outpatient visits and diagnostic tests, number and type of community health and social services, and the use of medications, aids and adaptations. Furthermore, respondents provided information on direct non-medical costs (including travel expenses) incurred by themselves and their caregivers, and reported number of days off work and gross loss of earnings, attributable to their health state or contacts with care providers. Resource use values were converted into costs by applying unit costs obtained from national databases such as the Department of Health's National Schedule of Reference Costs [11, 12], the PSSRU Unit Costs of Health and Social Care compendium,[13-15], the Annual survey of Hours and Earnings [16], the NHS supply chain catalogue [17] and the British National Formulary (BNF) [18] . Table II summarises the unit cost values and data sources for broader resource inputs.

Measurement and valuation of health outcomes

In line with the NICE reference case, the primary health outcome for the economic evaluation was the quality-adjusted-life-year (QALY) [8], which combines impacts on both health-related quality of life (HRQoL) and length of life [19]. HRQoLwas assessed using the EQ-5D-3L questionnaire (EQ-5D for brevity) [20] at baseline and at 3, 6 and 12 months post-randomisation. The EQ-5D comprises five dimensions: 'mobility', 'self-care', 'usual activities', 'pain/discomfort' and 'anxiety/depression. Responses in each dimension have 3 levels: (1) no problems; (2) moderate problems; and (3) extreme problems. EQ-5D health states can be converted into a single summary index by applying a utility algorithm, which attaches values to each permutation of responses to the EQ-5D descriptive system. We applied utility values for EQ-5D health states elicited from a general population sample in the UK using the time-trade-off method [21]. Utility values generated through this method range from -0.59 to 1.0; where 0 represents death, 1.0 represents full health and values below 0 indicate health states worse than death. QALY values for each patient were estimated by calculating the area under the baseline-adjusted utility curve, and were calculated using linear interpolation between baseline and follow-up utility scores.

Missing data

For the baseline analysis, multiple imputation under chained equations (MICE) [22] was used to model missingness for those cases where resource use or HRQoL data were unavailable, based on the tested assumption that data were missing at random. Regression models were used to impute unobserved costs and QALYs at each time point, and by treatment allocation, using age and gender as explanatory variables. Costs and EQ-5D utility scores at each time point contributed as both explanatory and imputed variables. The imputation was run 50 times following the rule of thumb that the number of imputations should be similar to the percentage of incomplete cases[22]. Fifty datasets were generated using predictive mean matching. Each imputed data set produced was independently analysed with bivariate regressions using a seemingly unrelated regression model to estimate the costs and QALYs in each treatment group over the 12-month trial horizon. Estimates from each imputed dataset were combined using Rubin's rule to generate overall mean costs and QALY estimates and their standard errors [23].

Analyses of resource use, costs and outcome data

Resource use items were summarised by treatment group and follow-up period and differences between groups were analysed using t-tests for continuous variables and chi-squared tests for categorical variables. Means and standard errors (SEs) for values of each cost category were estimated by treatment allocation and follow-up period and statistical differences in mean costs by treatment allocation were assessed using t-tests. Mean total costs by treatment allocation and follow-up period were also estimated. Statistically significant differences in the mean total costs were assessed using non-parametric bootstrapping, based on 10,000 replications.

For each of the five dimensions of the EQ-5D, we calculated the proportion of patients reporting sub-optimal function (moderate or extreme problems) and assessed differences between groups using chi-squared tests.

Cost-effectiveness analysis

Cost-effectiveness results were expressed in terms of an incremental cost-effectiveness ratio (ICER) and calculated by dividing the difference between treatments in mean total costs by the mean difference in total QALYs. The ICER represents the additional cost required to gain a QALY and in our case indicates whether investing additional resources on a particular type of fixation is cost-effective. As a general rule, NICE considers interventions costing the NHS less than £20,000 per QALY gained cost-effective [24]. To determine the level of sampling uncertainty around the ICER, we conducted non-parametric bootstrapping, generating 50,000 estimates of incremental costs and benefits [25]. The bootstrap replicates from the non-parametric bootstrapping were used to populate cost-effectiveness scatterplots. We calculated the net-monetary benefit (NMB) of using nail fixation versus locking plate fixation across three cost-effectiveness thresholds: £15,000 per QALY, £20,000 per QALY and £30,000 per QALY [26]. A positive incremental NMB indicates that the intervention is cost-effective compared with the alternative at the given cost-effectiveness threshold. Furthermore, cost-effectiveness acceptability curves (CEACs) were generated based on the proportion of bootstrap replicates with positive incremental net benefits. The CEACs indicate the probability that nail fixation is cost-effective relative to locking plate fixation across a range of cost-effectiveness thresholds.

Sensitivity and sub-group analyses

Several sensitivity analyses were undertaken to assess the impact of parameters with a degree of uncertainty on cost-effectiveness outcomes. These included: 1) restricting the analyses to complete cases (i.e. those with complete cost and outcome data over the 12-month follow-up period); 2) adopting a wider societal perspective that included private costs incurred by trial participants and their families, productivity losses and loss of earnings due to work absences; 3) estimating the cost-effectiveness under a per-treatment analysis; and 4) additionally adjusting the baseline analysis for pre-injury HRQoL, which was assessed using the EQ-5D at baseline.

Sub-group analyses were also conducted for the main cost-effectiveness results to explore heterogeneity in the trial population. These were conducted by: (i) age group (<50 and ≥50 years) and (ii) gender (male, female).

Longer-term economic modelling

The study protocol allowed for decision-analytic modelling to estimate the cost-effectiveness of intramedullary nail fixation over a longer-term time horizon, drawing on best available secondary data sources, supplemented where necessary by expert opinion. Use of a lifelong time horizon may be warranted in cost-effectiveness analysis when there is reason to expect differences in long-term costs and QALYs. Factors that could affect either include differences in life expectancy, HRQoL, and rehospitalisation or reoperation rates.

Beyond the 12-month follow-up period assessed in this study, rehospitalisation and reoperation are possible due to excess complications [3]. We conducted a preliminary analysis of the extended follow-up data for this trial to determine whether differences in HRQoL outcomes, metalwork removal and in rates of complications persisted at 24 months. Furthermore, we systematically searched external studies that compared plate and nail fixation for evidence on clinically important differences beyond 12-months post-surgery. Though we did not find good quality external evidence, analysis of the composite of available data indicates that, beyond 12 months, rates of deep infection and wound healing are similar [2, 3, 27]. According to a recent analysis of 358 patients in Belgium, total length of stay in hospital (due to initial surgery and reoperations) and rate of deep infections are the major cost-drivers of tibial shaft fractures [28]. The combined evidence thus indicated that clinical and economic differences between nail and plate fixation are likely concentrated in the first year following surgery. This informed our decision not to undertake longer-term economic modelling.

Results

Between April 2013 and February 2016, 321 patients were recruited and randomised (nail fixation = 161; locking plate = 160). Three patients did not complete the baseline questionnaires. A total of 276 patients completed the 3-month questionnaire whilst 284 and 258 patients returned questionnaires at the 6- and 12-month follow-up time points, respectively. Overall, the follow-up rate was greater than 80% at all time-points. The trial results based on the primary clinical outcome measure, as well as details on time to union, postoperative complications at the 6-week assessment, and the number and type of further surgical interventions associated with the fracture in each group within 12 months of initial surgery, are presented elsewhere [7]. Table III shows the volume of missing health economic data by treatment allocation and follow-up time point. The missing data pattern was non-monotonic since several individuals with missing data at one follow-up time point completed subsequent questionnaires.

Resource use

Resource use was generally higher for participants allocated to the locking plate group compared to those allocated to nail group, but this was not always statistically significant (Table A1; Appendix). The exceptions, which showed statistically significant differences, were the mean total inpatient stay between 3-6 months (0 (nail) vs. 0.11 (locking plate) days), and mean total outpatient care contacts between 3-6 months (3.64 vs. 4.78 contacts). The differences in outpatient care appear to be driven by increased physiotherapy contacts in the locking plate group (1.84 vs. 2.53 visits).

Costs

The mean intervention costs from admission until discharge were £5460 for nail fixation compared to £5600 for locking plate fixation; the mean difference of £140 (CI: -684.24 to 262.61; *P*=0.19) (table IV) The mean length of the initial hospital stay was 3.87 days (*SE* 0.34) for nail fixation vs. 3.85 days (*SE* 0.33) for locking plate fixation. The mean total NHS and PSS cost throughout the first 6 months post-randomisation was £5876 for nail fixation and £6814 for locking plate fixation; the mean cost difference of £939 was statistically significant at the 5% significance level (*P*=0.04). The mean total NHS and PSS cost for the entire 12-month follow-up period was £6107 for nail fixation and £7102 for locking plate fixation; the mean cost difference of £995 was statistically significant at the 10% significance level (*P*=0.05). Productivity losses to employers through sickness absences appeared higher in the locking plate arm, and the difference for the entire follow-up period was statistically significant at the 10% level. Overall societal costs, for the entire follow-up period, were on average £3396 higher in the locking plate group; this cost difference was statistically significant at the 5% level (*P*=0.01) (table V)

Health-related quality of life outcomes

Table A2 (Appendix) summarises the number and proportion of reported problems for each level for each dimension of the EQ-5D. The proportion of trial participants reporting suboptimal function is also indicated for each dimension and the difference between the two treatment arms shown using p-values. With the exception of mobility at 3 months (81% nail vs. 89% locking plate), which was statistically significant at the 10% significance level, there were no significant differences in the proportions of individuals reporting sub-optimal function within dimensions between the two arms at each time point.

The EQ-5D utility scores pre-injury, post-injury (baseline) and at 3-, 6- and 12 months post-randomisation are shown in table VI and figure 1. Both groups showed improvement in HRQoL from baseline to the last follow-up point. The most notable difference was observed at 6 months post-randomisation with a higher utility value observed for the nail fixation group (*P*=0.03).

The mean total QALYs (imputed) over the 12 months for IM nail and locking plate fixation were 0.55 and 0.54 respectively, but the difference was not statistically significant (0.01 QALYs, 95% CI: -0.03 to 0.06; *P*=0.56).

Cost-effectiveness analysis

The baseline economic evaluation, using imputed attributable costs and QALYs and covariate adjustment, indicated that intramedullary nail fixation was associated with significantly lower mean NHS and PSS costs (-£970 (95% CI: -1685 to -256) and a non-statistically significant increase in QALYs (0.01 QALYs, 95% CI: -0.03 to 0.06) over the entire 12-month follow-up period (table VII). Uncertainty surrounding the ICER estimates are represented graphically in the cost-effectiveness plane (figure 2), which shows that most simulated ICER values fall in the south-east quadrant, indicating that nail fixation is on average less costly and more effective (produced more QALYs). The probability of cost-effectiveness given the uncertainty surrounding the mean ICER value is visually displayed in the CEAC. The probability that nail fixation is cost-effective ranged between 94-98% across cost-effectiveness thresholds of £15,000-£30,000 per QALY (table VII; figure 3). The net-monetary benefit for IM nail, for the base case, was positive (incremental NMB values>£1200).

Sensitivity and sub-group analyses

Most of the sensitivity analyses undertaken (complete case, societal perspective, and imputed attributable costs and QALYs additionally controlled for pre-injury utility) supported the base case finding (table VII). However, the per-treatment analysis showed a slightly different pattern for QALY outcomes. The results for that analysis indicated that participants in the nail fixation arm, on average, experienced slightly worse QALY outcomes (-0.01 QALYs (95% CI -0.06 to 0.04)). However, the result was not statistically significant. Moreover, the cost difference remained in the same direction (-875 (95% CI -1725 to -26)) as that for the base case analysis. The results of the sub-group analyses indicate that in the sample of patients below the age of 50, nail fixation was the dominant intervention; it lowered costs and moderately increased QALYs on average (table VII). In patients over the age of 50 years, nail fixation was associated with lower costs (-£821) and lower benefits (-0.022 QALYs), on average, compared to locking plate fixation. However, the 95% confidence intervals for both the incremental cost (95% CI -2760 to 1110) and QALY (95% CI -0.09 to 0.05) estimates suggest considerable uncertainty surrounding the effects of intramedullary nail fixation for this older group of patients.

Discussion and Conclusion

This study shows that nail fixation ‘dominates’ locking plate fixation in health economic terms. This conclusion is driven by the finding that there was a modest QALY gain in the nail group over the 12-month time horizon of the trial and costs were significantly lower in the nail group. In addition, there was a high probability that nail fixation is cost-effective across cost-effectiveness thresholds recommended by decision-makers, a finding that remained robust to most sensitivity and sub-group analyses. The main exception to this pattern of results was the sub-group of patients above 50 years in whom nail fixation was associated with a reduction in costs, but also marginally lower QALYs, although there was substantial uncertainty around the estimates. A retrospective review of forty-two patients (>50 years old) found that older patients sustaining tibial shaft fractures treated with intramedullary nailing take longer to heal, and require more procedures to achieve union [29]. This external evidence suggests that other factors may need to be taken into account when deciding the optimal treatment approach for distal tibia fractures in the elderly.

To our knowledge, this is the first trial-based economic evaluation to compare the cost-effectiveness of these two surgical procedures for the treatment of distal tibia fractures. Previous studies have compared two types of intramedullary nails (reamed vs. unreamed) in treating closed and open tibia fractures; however, they did not compare intramedullary nails to other interventions [5]. Busse and colleagues reported costs associated with treatment of low-energy tibial fractures with either casting, casting with therapeutic ultrasound, or intramedullary nailing (with and without reaming) by use of a decision tree model [30]. The results of that analysis indicated that intramedullary nailing was the treatment of choice for closed and open grade I tibial shaft fractures; however, impact on HRQoL was not assessed. Kao et al conducted a cost-effectiveness analysis comparing conventional buttress or dynamic compression plates and locking plates for treating displaced distal tibial fractures, but did not conduct a comparative assessment with intramedullary nails [6]. The same interventions have been compared in different clinical contexts, for example, for the treatment of midshaft clavicle fractures [31, 32]; however the cost-effectiveness evidence in those contexts remains limited [33].

Strengths of the current economic evaluation include data collected from a prospective randomised trial with frequent assessments over a 12-month follow-up period and minimal loss to follow-up. This enabled a trial-based economic evaluation that was rigorous, with effectiveness and cost measures (including indirect patient-reported costs) collected prospectively, and the direct measurement of utility scores from our study participants to calculate QALYs [34]. Furthermore, the economic evaluation was conducted according to nationally agreed design and reporting guidelines [35].

Limitations of this trial-based economic analysis include that long-term cost-effectiveness beyond the 12-month follow-up period was not assessed. However, preliminary analysis of the HRQoL outcomes of the trial participants using extended follow-up data for this trial indicates that EQ-5D utility scores for the nail fixation and locking plate groups remain similar at 24 months post-randomisation (extended follow-up data will be reported in due course). In addition, by 12 months, rates of metalwork removal, revision fixations and other secondary operative procedures were similar between the locking plate and nail fixation groups [7].The indication, therefore, is that the benefits of nail fixation are very likely to be concentrated in the first year that follows the treatment of displaced, extra-articular fractures of the distal tibia. Furthermore, our systematic search for external studies that compared plate and nail fixation did not find any good quality evidence on differences in functional outcomes and HRQoL beyond 12 months post-surgery. The available studies were either based on short follow-up periods,[36] small sample sizes,[2] non-randomised studies that relied on retrospective reviews or case series which tend to suffer from selection biases, [2, 37] or a combination of these factors. A second potential limitation is that we used NHS tariffs to estimate total cost of the surgical treatment, which some have argued do not fully capture the cost of orthopaedic procedures and may not take into account varying operating theatre times [38, 39]. However, in our case, it is unlikely that a different costing approach would have shifted results in favour of the locking plate as the mean operating theatre times were the same (124mins) for both procedures and the cost of implants represented a relatively minor component of total costs.

In conclusion, our study provides a comprehensive assessment of the cost-effectiveness of two commonly undertaken treatments for distal tibia fractures with obvious implications for the orthopaedic community. Notwithstanding the limitations of within-trial analyses, this study provides robust evidence that over the first year that follows surgery, nail fixation is a cost saving intervention without detriment to health-related quality of life outcomes. Given these results, there is economic justification for recommending nail over locking plate fixation for the management of extra-articular distal tibia fractures.

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Table I: Unit costs (£, 2014-15 prices) associated with initial operative procedures and initial hospital stay for intramedullary nail and locking plate fixation

Item	Unit Cost	Source
Surgery Costs[1]		
Average surgery cost of distal tibia fracture fixation (based on mean length of stay of 5 days[2])	£ 5,315.47	National schedules of Reference Costs year 2014-15 - 'Major Knee Procedures for Trauma, 19 years and over, with CC Score 0'-**HT23D[11]**
Cost per excess bed day	£ 327.00	National schedules of Reference Costs year 2014-15 - 'Major Knee Procedures for Trauma, 19 years and over, with CC Score 0'-**HT23D[11]**
Implants: Intramedullary nail fixation		
Guide wire 3.2x300	£43.11	UHCW[3]
Reaming rod 2.5x1000	£63.47	UHCW
Distal bolts	£45.88	UHCW
End cap	£37.93	UHCW
Blocking Screw	£29.80	UHCW
Nail	£265.53	UHCW

[1]HRG Code for distal tibia fracture fixation is similar for both intramedullary and locking plate fixation
[2] Surgery cost from NHS Reference Costs is based on assumed mean length of stay of 5 days for this category of patients; adjustments were made for all patients who stayed in hospital for a period less than 5 days; detailed methodology explained in-text.
[3] UHCW denotes University Hospitals Coventry and Warwick NHS Trust Finance Department

Table II: Summary of unit cost values (£, 2014-15 prices) and data sources

Resource item	Unit cost	Unit of analysis	Source of unit cost
Subsequent inpatient care			
Orthopaedics (your leg)			
Cost per average LoS[4] of 1 day	£1,780.34	per procedure	NHS Reference Costs 2014-2015, 'Minor Knee Procedures for Non-Trauma, 19 years and over' - **HN25A[11]**
Day Case	£1,349.10	per procedure	
Orthopaedics (any other bones)			
Cost per average LoS of 4 days	£2,648.56	per procedure	NHS Reference Costs 2014-2015, 'Other Muscle, Tendon, Fascia or Ligament Procedures' - **HN93Z[11]**
Day Case	£965.19		
Adjustment per day ± avg. LoS (excess bed days)	£278.52	per day	NHS Reference Costs 2014-2015, 'Other Muscle, Tendon, Fascia or Ligament Procedures' - **HN93Z[11]**
Other Inpatient			
Rehabilitation Unit	£335.00	per session	NHS Reference Costs 2013-2014, 'Rehabilitation for other trauma', **V636Z[12]**
Outpatient Care			
Orthopaedics	£112.50	per session	Reference Costs 2014-2015 [11]
Blood tests/ Phlebotomy	£3.00	per test	Reference Costs 2014-2015 [11]
X-rays	£30.23	per test	Reference Costs 2014-2015[11]
MRI scan	£146.00	per test	Reference Costs 2014-2015[11]
CT scan	£111.00	per test	Reference Costs 2014-2015[11]
Hospital Physiotherapist (NHS)	£38.00	per session	PSSRU 2015 pg.217 [13]
Physiotherapist (private)	£70.00	per hour	http://www.thephysiocentre.co.uk/how_much/
Emergency department (orthopaedics & trauma)	£112.50	per session	Reference Costs 2014-2015 [11]
Emergency department other	£140.59		Reference Costs 2014-2015[11]
Primary and community care			
General Practitioner surgery consultation	£225.00	per hour	PSSRU 2015 pg. 178[13]
General Practitioner home visit	£5.20	per home visit minute	PSSRU 2010 pg. 167[15]
General Practitioner phone call	£27.00	per telephone consultation lasting 7.1 minutes	PSSRU 2015 pg. 178[13]
Practice nurse	£56.00	per hour of face-to-face contact	PSSRU 2015 pg. 174[13]

[4] LoS denotes length of stay

Resource item	Unit cost	Unit of analysis	Source of unit cost
District nurse	£67.00	per hour of patient related work	PSSRU 2015 pg. 169[13]
Community Physiotherapist	£36.00	per hour of consultation	PSSRU 2015 pg. 179[13]
Occupational therapist	£44.00	per hour	PSSRU 2015 pg. 191[13]
Personal Social Services			
Meals on wheels (frozen, daily)	£46.00	per weekly meal	PSSRU 2014 pg. 127[14]
Meals on wheels (hot, daily)	£44.00	per weekly meal	PSSRU 2014 pg. 127[14]
Laundry services	£4.55	per load	North Yorkshire Country Council http://www.northyorks.gov.uk/article/23988/Paying-for-social-care-services-in-the-community
Social worker contacts	£42.00	per hour	PSSRU 2015 pg. 95[13]
Care worker contacts including help at home	£24.00	per hour	PSSRU 2015 pg. 192[13]
Aids and Adaptations			
Crutches	£5.06	per unit	NHS supplies catalogue 2015/16[17]
Stick	£3.94	per unit	NHS supplies catalogue 2015/16[17]
Zimmer frame	£35.99	per unit	NHS supplies catalogue 2015/16[17]
Grab Rail	£1.61	per unit	NHS supplies catalogue 2015/16[17]
Dressing aids	£1.66	per unit	NHS supplies catalogue 2015/16[17]
Long handle shoe horn	£1.66	per unit	NHS supplies catalogue 2015/16[17]
Productivity losses			
Median wage rate (full-time males)	£567.00	per week	Annual survey of hours and earnings (ASHE, 2015)[16]
Median wage rate (full-time females)	£471.00	per week	ASHE, 2015[16]
Median wage rate (part-time males)	£156.00	per week	ASHE, 2015[16]
Median wage rate (part-time females)	£171.00	per week	ASHE, 2015[16]
Median earnings (self-employed)	£10800.00	per year	https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/500317/self-employed-income.pdf

Table III Number and proportion of individuals with missing health economic data by treatment allocation

Variable	Description	Missing values: N (%)		
		Nail (N=158)	Locking Plate (N=160)	Total
eq5db	EQ-5D index score pre-injury	1 (1%)	1 (1%)	2 (1%)
eq5d0	EQ-5D index score post-injury	2 (1%)	3 (2%)	5 (2%)
eq5d1	EQ-5D at 3 months	23 (15%)	19 (12%)	42 (13%)
eq5d2	EQ-5D at 6 months	16 (10%)	18 (11%)	34 (11%)
eq5d3	EQ-5D at 12 months	43 (27%)	42 (26%)	85 (27%)
c0	Operative costs (surgery cost including initial hospital stay + implants)	0 (0%)	0 (0%)	0 (0%)
c1	Total resource use baseline - 3 months	54 (34%)	54 (34%)	108 (34%)
c2	Total resource use between 3- 6 months	30 (19%)	31 (19%)	61 (19%)
c3	Total resource use between 6-12 months	60 (38%)	58 (36%)	118 (37%)
c4	Total resource use between 0- 6 months	67 (42%)	62 (39%)	129 (41%)
c5	Total resource use between 0-12 months	88 (56%)	82 (51%)	170 (54%)

Table IV NHS and personal social service costs for cases with complete data by trial allocation, study period and cost category (£, 2014-15 prices)

Cost category by period	Nail Mean (SE) Cost	Locking Plate Mean (SE) Cost	Mean Difference	P Value [a]	Bootstrap 95% CI [b]
0-6months (n = 189 total; n= 91 IM; N=98 LP)					
Initial operation cost	5460.04 (137.92)	5600.11 (137.92)	-140.07	0.19	(-684.24 to 262.61)
Subsequent inpatient care	40.73 (29.35)	313.14 (187.55)	-272.41	0.08	(-648.97 to 104.13)
Outpatient care	218.66 (11.46)	249.01 (19.49)	-30.35	0.09	(-75.00 to 14.31)
Community care	106.91 (28.42)	601.69 (371.42)	-494.78	0.10	(-1233.98 to 244.42)
Medications	37.73 (10.18)	38.83 (14.28)	-1.11	0.47	(-35.73 to 33.52)
Personal social services	0.52 (0.52)	0.98 (0.59)	-0.46	0.28	(-2.02 to 1.10)
Aids and adaptations	10.97 (2.30)	10.45 (1.61)	0.52	0.58	(-5.02 to 6.06)
Total costs throughout first 6 months	***5875.56 (124.85)***	***6814.22 (425.71)***	***-938.66***	***0.04****	***(-1795.46 to -83.62)***
0-12months (n = 160 total; n= 70 IM; N=78 LP)					
Initial operation costs	5428.47 (112.00)	5528.72 (114.25)	-100.26	0.53	(-671.23 to 298.66)
Subsequent inpatient care	234.91 (92.68)	596.25(237.18)	-361.34	0.16	(-848.35 to 211.12)
Outpatient care	268.94 (16.90)	299.14 (26.25)	-30.20	0.34	(-100.29 to 27.88)
Community care	107.09 (23.30)	588.22 (410.64)	-481.13	0.25	(-1401.81 to 361.51)
Medications	58.14 (19.60)	78.45(35.95)	-20.31	0.62	(-111.91 to 62.76)
Personal social services	0.32 (0.32)	0.91 (0.64)	-0.59	0.40	(-2.16 to 0.88)
Aids and adaptations	9.45 (2.08)	10.77 (1.89)	-1.28	0.65	(-7.90 to 2.03)
Total costs throughout first 12 months	***6107.32 (158.56)***	***7102.46 (485.18)***	***-995.14***	***0.05***	***(-2069.63 to -74.93)***

[a] P value calculated using student t-test, 2 tail unequal variance
[b] Non-parametric bootstrap estimation using 1,000 replications

Table V: Societal costs related to distal fracture fixation for cases with complete data by treatment arm (£, 2014-15)

Cost category by period	**Nail Mean (SE) Cost**	**Locking Plate Mean (SE) Cost**	**Mean Difference**	**P Value [a]**
Follow up-period: 0 – 6 month				
NHS and PSS costs	5875.56 (124.85)	6814.22 (425.71)	-938.66	0.04
Private costs	16.36 (8.02)	12.46 (3.74)	3.90	0.65
Cost of lost productivity	3901.13 (759.48)	5351.80 (814.56)	-1450.67	0.20
Societal costs	**9793.05 (761.66)**	**12178.48 (1003.33)**	**-2385.43**	**0.07**
Follow-up period: 0 – 12 months				
NHS resource use costs	6107.32 (158.56)	7102.46 (485.18)	-995.14	0.05
Private costs	49.52 (35.72)	24.65 (7.80)	24.87	0.48
Cost of lost productivity	3333.28 (649.45)	5758.62 (1032)	-2425.34	0.05
Societal costs	**9490.12 (658.07)**	**12885.73 (1174.33)**	**-3395.61**	**0.01**

[a] P value calculated using student t-test, 2 tail unequal variance

Table VI Mean EQ-5D index scores at the baseline and follow-ups: nail vs. locking plate for distal tibia fixation

	Intramedullary Nail		Locking Plate		Difference (95%CI)		
Time point	**Mean (SD)**	**n**	**Mean (SD)**	**n**	**Raw**	**Adjusted***	**p-value**
Post-injury	-0.003 (0.334)	158	-0.024 (0.311)	156	-0.021	-0.030 (-0.09 to 0.03)	0.331
3 months	0.546 (0.273)	134	0.499 (0.302)	142	-0.047	-0.058 (-0.12 to 0.00)	0.067
6 months	0.670 (0.265)	143	0.622 (0.275)	141	-0.048	-0.064 (-0.12 to -0.01)	0.029
12 months	0.722 (0.278)	128	0.731 (0.246)	130	0.009	-0.018 (-0.07 to 0.05)	0.525

*Mixed effects regression model based on intention to treat analysis approach. Fixed effects were allocated treatment group, age group, baseline pre-injury score and gender, and recruiting site was a random effect.

Table VII: Cost-effectiveness, cost/QALY (£, 2015): intramedullary nail fixation compared to locking plate fixation

	Incremental cost (95% CI)	Incremental QALYs (95% CI)	ICER *	Probability of cost-effectiveness			Net monetary benefits		
				P^1	P^2	P^3	NMB^1 (95% CI)	NMB^2 (95% CI)	NMB^3(95% CI)
Base Case									
Imputed attributable costs and QALYs, covariate adjusted	-970 (-1685 to -256)	0.01 (-0.03 to 0.06)	Dominant	0.98	0.97	0.94	1204 (43 to 2465)	1273 (-82 to 2689)	1410 (-385 to 3190)
Sensitivity analyses									
Complete case attributable costs and QALYs, covariate adjusted	-1791 (-3986 to -225)	0.04 (-0.02 to 0.09)	Dominant	0.99	0.98	0.98	1429 (146 to 2818)	1558 (118 to 3069)	1818 (36 to 3626)
Societal perspective	-2230 (-4626 to 167)	0.014 (-0.03 to 0.06)	Dominant	0.97	0.97	0.96	2423 (-26 to 5173)	2493 (-93 to 5337)	2626 (-270 to 5706)
Per treatment analysis – imputed attributable costs and QALYs, covariate adjusted	-875 (-1725 to -26)	-0.01 (-0.06 to 0.04)	172857 (south-west quadrant)	0.92	0.88	0.81	923 (-347 to 2353)	909 (-570 to 2508)	872 (-1032 to 2861)
Imputed attributable costs and QALYs, additionally controlling for pre-injury utility	-1188 (-2266 to -110)	0.02 (-0.02 to 0.06)	Dominant	0.99	0.99	0.98	1518 (212 to 2940)	1633 (180 to 3194)	1862 (66 to 3738)
Subgroup analyses									
Base Case: age <50	-1468 (-3547 to -291)	0.08 (0 to 0.17)	Dominant	0.99	0.98	0.98	1730 (207 to 3320)	1953 (166 to 3804)	2402 (55 to 4830)
Base case: age ≥50	-821 (-2760 to 1110)	-0.022 (-0.09 to 0.05)	60000 (south-west quadrant)	0.71	0.67	0.62	709 (-1960 to 3480)	630 (-2320 to 3610)	473 (-3065 to 3930)
Base Case: males	-1651 (-5042 to -682)	0.05 (-0.07 to 0.17)	Dominant	0.71	0.68	0.62	745 (-1945 to 3612)	670 (-2305 to 3741)	520 (-3043 to 4075)
Base Case: females	-1193 (-5243 to 102)	0.02 (-0.05 to 0.10)	Dominant	0.71	0.68	0.62	746 (-1950 to 3643)	673 (-2307 to 3781)	529 (-3049 to 4157)

*ICER: Incremental cost-effectiveness ratio; dominance indicates average costs were less and average benefit greater for intramedullary nail vs. locking plate fixation
P^1, P^2, P^3: probability cost-effective if willing to pay £15,000/QALY, £20,000/QALY or £30,000/QALY, respectively
NMB^1, NMB^2, NMB^3: net monetary benefit if willing to pay £15,000/QALY, £20,000/QALY or £30,000/QALY, respectively