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Title: A retrospective, longitudinal study of the healthcare resource utilisation and costs among patients with and without infection following intramedullary nailing for a tibial shaft fracture in England

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Running head:

Resource use and costs in patients with and without infection after tibial fracture nailing

Key words:

- Tibial shaft fracture
- CPRD
- HES
- Infection
- Cost
- England

- Trauma
- Burden of disease

Abstract

Objectives

To determine the impact of infections on direct costs and healthcare resource use in England for patients undergoing intramedullary nailing (IMN) for tibial shaft fractures.

Design

A retrospective longitudinal (2 year) cohort study.

Setting

England.

Participants

The study population included adult patients (≥18 years) in England with a diagnosis of tibial shaft fracture (ICD-10, S822) in the inpatient setting between May 2003 and June 2017 followed by a procedure for IMN for tibial shaft fracture within 30 days. Patient data were derived from the Clinical Practice Research Datalink (CPRD) linked to NHS Hospital Episode Statistics datasets.

Primary independent variable

Infection.

Primary and secondary outcome measures

The primary outcome measure was total inpatient costs from index stay admission through one-year of follow-up. Secondary outcome measures included cumulative total healthcare costs, and resource utilisation at 30 days, 90 days, 1 year and 2 years.

Results

805 patients met the inclusion criteria. At the index inpatient stay, 3.7% had a post IMN infection, rising to 11.7% at 1-year. One-year inpatient costs were 80% higher for patients with infection ($p<0.001$). Total costs were estimated to be £14,756 (95% confidence interval [CI]; £13,123, £16,593) for patients with infection versus £8,279 (95% CI; £7,946, £8,626). Length of stay (LOS), readmission, and reoperation were the key drivers of healthcare costs (all $p<0.001$). After adjustment, LOS was higher by 109% (95% CI: 62%, 169%), from 10.5 days to 21.9 days, for patients with infection. The odds of being readmitted or requiring reoperation were higher by 5.18 times (95% CI: 3.01, 9.13) and 2.47 times (95% CI: 1.48, 4.09), respectively, for patients with infection versus those without infection.

Conclusions

Post IMN infection significantly increases inpatient costs, LOS, readmissions, and reoperations associated with tibial fracture fixation. Healthcare burden could be reduced through novel surgical site infection prevention strategies.

Strengths and limitations of this study

- This is the first study to quantify the healthcare resource burden of infections following tibial shaft fractures treated with intramedullary nailing in England.
- The study had a long term and cross-sector perspective that included inpatient, hospital outpatient and primary care parameters.
- This study only considered patients with complete follow-up, thus excluding very severe patients with short life expectancy.
- Some costs were not directly available from the CPRD dataset and were sourced from published national sources.

- The study relied on clinical codes to identify superficial and deep infections which may be subject to coding errors and misclassifications.

Introduction

Tibial shaft fractures are the most common type of long-bone fracture. They can be either closed fractures, where the skin remains intact, or open fractures (accounting for 25% of all tibial shaft fractures) where the skin is broken (1).

Intramedullary nailing is a common surgical treatment for the fixation of the fractured bone: an intramedullary nail is inserted through the top of the tibia, into the inner cavity, and held in place with screws (1). Nailing allows preservation of the soft tissues surrounding the fracture site (1), and provides the greatest mechanical stability (2). In addition, as the nail is load-sharing rather than load-bearing, intramedullary nailing permits earlier weight-bearing on the fractured limb than other surgical treatments (3).

Infection after intramedullary nailing is a potential complication, especially in severe open fractures, that can delay wound healing and fracture repair (2, 4-6). If left untreated, an infection may lead to permanent loss of function of the affected limb (2, 4, 7). Open fractures are especially prone to infection (over 31% of cases based on a meta-analysis (6)) due to wound exposure to the environment with the risk of infection depending on the severity of soft tissue damage (5). Patients with cases of extreme and uncontrollable infection may require limb amputation to prevent deterioration and maintain quality of life (2).

Infections following fracture fixation are subclassified according to the depth of the infection: superficial (subcutaneous region), deep (muscle/fascial region), or organ/space infections (8). However, there is debate over the usefulness of these terms, as they can be arbitrary depending on the location of an infection (7). A US study reported an infection rate of 2% after intramedullary nailing for closed fractures compared with 7.1% for open fractures (9). A Spanish

study reported an infection rate of 2.7% in closed fractures compared with 19% in open fractures (10). In a meta-analysis of studies investigating prophylactic antibiotic use in patients with open tibial fractures treated with intramedullary nailing, the risk of infection increased with severity of the fracture, rising to over 31% among patients with the most severe injury (and who received systemic antibiotics only) (6).

Patients who experience infection are more likely to require additional surgeries, extended hospital stays, and extensive treatment for post-operative infection (2, 4, 5, 7). There are only a limited number of studies, however, which compare healthcare resource utilisation and treatment costs for tibial shaft fractures with and without post-surgical infection across Europe. In a Belgian study, healthcare costs were five times higher and total length of hospital stay (LOS) six times longer for open tibial shaft fracture patients with deep infection versus those with no infection (11). In Denmark, the average direct cost of treating a severe open tibial shaft fracture was estimated to be €49,817, increasing to €81,155 when infection occurred. In patients treated within 7 days of their injury, infection increased the average direct cost and LOS by 124% and 135%, respectively (12).

The aim of this study was to determine the impact of infections on healthcare costs and resource utilisation for patients undergoing intramedullary nailing for tibial shaft fractures from the perspective of National Health Service (NHS) England.

Materials and methods

Study design and setting

This was a retrospective longitudinal cohort study of patients in England who underwent intramedullary nailing for tibial shaft fracture (open or closed) followed-up for 2 years. Data derived from the Clinical Practice Research Datalink (CPRD) linked to NHS Hospital Episode Statistics (HES) and NHS Reference costs were used to calculate costs and healthcare

resource utilisation associated with infections (superficial or deep) following intramedullary nailing.

The CPRD database is an anonymised longitudinal dataset of over 11.3 million medical records from over 600 primary care practices across the UK (13). It includes all visits to primary care and other healthcare professionals, reasons for visits, diagnoses observations, medical history, test results, referrals, and prescriptions (13). For this study, HES data relating to admissions to, or attendances at, English NHS healthcare providers was used (HES Admitted Patient Care data).

Patients

The study population included adults (aged ≥18 years) who were diagnosed with a tibial shaft fracture (ICD-10 code: S82.2) between May 2003 and June 2017 and who subsequently underwent intramedullary nailing within 30 days of diagnosis. Inclusion and exclusion criteria and patient attrition flow are depicted in Figure 1.

Infections were identified using clinical diagnosis codes either from the inpatient setting (ICD-10, OPCS codes) or the primary care setting (Read codes) (See Additional file 1). Only patients with an infection occurring on (or after) Day 2 following the index date were considered eligible for the infection cohort, as this would exclude infections that were present pre-operatively. For subgroup analysis, diagnosis codes were categorised into either deep or superficial infections and open or closed fractures based on medical knowledge.

Data collection

The primary outcome of this study was total inpatient costs (Healthcare Resource Group [HRG], unbundled HRG and specialised care) accrued beginning from index stay admission through one-year of follow-up post-discharge from the index stay. Secondary endpoints included cumulative total healthcare costs and resource utilisation for 30 days, 90 days, 1 year and

2 years of follow-up post discharge of the index stay. Total healthcare costs comprised inpatient, hospital outpatient and primary care costs (consisting of consultations, prescriptions, and tests/investigations). Healthcare resource utilisation included LOS, readmissions, reoperations, days in intensive care unit (ICU), hospital outpatient visits, diagnostic tests, and primary care visits. Time to infection was an additional secondary outcome.

Resource use and costs

Healthcare cost data were estimated based on the healthcare resource utilisation reported in CPRD/HES and the unit cost associated with each service.

Inpatient costs

The 2017/2018 HRG Reference Costs Grouper software was used to generate HRG codes for each inpatient admission (14, 15). Each HRG code was assigned an appropriate cost from NHS Reference Costs (16), using admission method, LOS, trim point and the patient classification to associate the relevant costs (14, 17, 18). Inpatient stays were considered as long-stays for admissions lasting ≥2 days in line with NHS reference costs (17, 19). Unbundled HRGs were automatically generated by the Grouper software and assigned relevant costs (16). Specialised care episodes were identified using the Prescribed Specialised Services Tool 2017/18 software and top-up costs were applied as a percentage increase to the HRG cost (20).

Hospital outpatient costs

Outpatient costs were derived from the CPRD referral file where the referral type was classified as “outpatient” and matched against NHS reference costs for the same or closest matching specialty (16, 18).

Primary care costs

Consultations from the CPRD consultations file were categorised based on the setting (clinical, surgery, home, telephone, administrative) and healthcare provider (doctor, nurse, other professional). Costs were sourced from the Unit Costs of Health and Social Care (21).

Laboratory and diagnostic tests from the CPRD tests file were manually matched to the closest NHS test category and assigned NHS Reference Costs (17).

Medication categories were based on British National Formulary classifications as recorded in the CPRD therapy file, and unit costs were obtained using the Prescription Cost Analysis 2017 using the mean sub-paragraph cost associated with each medication (22).

Follow-up period and cohort definitions

Follow-up time was calculated as the difference between the index discharge date and the last date of observation. Only patients with follow-up data at the relevant time point were included in the analysis.

Statistical analyses

All analyses were conducted using R Studio v3.4.3. Statistical significance was set a priori at $p<0.05$ (two-sided). Study variables were analysed descriptively. Time-to-infection was depicted graphically using the Kaplan-Meier estimator. Unadjusted comparisons of patient demographics, comorbidities, and medication use between groups were performed using t-tests for continuous variables that were approximately normal, and Wilcoxon rank sum tests for continuous variables that were not normally distributed. Pre-specified subgroup analyses allowed for stratification of results according to type of fracture (open versus closed) or type of infection (superficial versus deep).

Generalised Linear Models were used to adjust for confounding. Covariates were identified a priori as risk factors for the study outcomes based on clinical knowledge. A backwards stepwise

procedure was applied according to Akaike information criterion. Missing data were not imputed. Except for in the sensitivity analyses, patients with missing data were excluded from analyses.

Sensitivity analyses at all time points were conducted using data from the subgroup of patients who had complete two-year follow-up for total costs, LOS, readmission (rate and mean count), and reoperation (rate and mean count).

Patient and public Involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Results

Patient baseline characteristics

Of the 10,825 patients identified as having suffered a tibial shaft fracture, 3,005 received intramedullary nailing. Of these, a total of 805 patients met the inclusion criteria and were included in the study (Figure 1). The mean follow-up time was 4.8 years. The mean (standard deviation [SD]) age was 40.8 (17.2) (See Table 1 for index stay; Additional file 2). A majority of patients were male (n= 590; 73.3%) and most had suffered a closed (n=663; 82.4%) tibial shaft fracture. Among patients with an open fracture, a significantly higher proportion of patients (10.6%) experienced an infection compared with 2.3% of patients with a closed fracture (p<0.001; Table 1).

Figure 1. Patient screening and enrolment according to the study inclusion/exclusion criteria

Table 1. Patient demographic and clinical characteristics (index stay and 1-year analysis cohorts)

	All enrolled patients (N=805)	Index stay		
		No infection (N=775)	Infection (N=30)	p-value
Demographics				
Age (years), mean (SD)	40.8 (17.2)	40.7 (16.8)	43.0 (23.9)	0.61
Gender, n (%) Male	590 (73.3)	569 (73.4)	21 (70.0)	0.84
Clinical history/comorbidities				
Charlson score, mean (SD)	0.04 (0.23)	0.04 (0.24)	0.00 (0.00)	<0.001
Smoker, n (%)	256 (31.8)	247 (31.9)	9 (30.0)	0.99
Diabetes, n (%)	27 (3.4)	27 (3.5)	0 (0.0)	0.62
COPD, n (%)	8 (1.0)	8 (1.0)	0 (0.0)	1.00
Congestive heart failure, n (%)	2 (0.3)	2 (0.3)	0 (0.0)	1.00
Hypertension, n (%)	12 (1.5)	12 (1.6)	0 (0.0)	1.00
Compartment syndrome, n (%)	27 (3.4)	22 (2.8)	5 (16.7)	<0.01
Index episode				
Inpatient waiting time (days) for surgery, mean (SD)	1.4 (2.4)	1.4 (2.4)	0.70 (2.4)	0.14
Fracture type, n (%) Open fracture	142 (17.6)	127 (16.4)	15 (50.0)	<0.001
Received ≥1 prescription for antibiotics in the 12 months prior to the index stay, n (%)	60 (7.5)	60 (7.7)	0 (0.00)	0.16
Received ≥1 prescription for opioids in the 12 months prior to the index stay, n (%)	16 (2.0)	15 (1.9)	1 (3.3)	0.46

Abbreviations: COPD, chronic obstructive pulmonary disease; SD, standard deviation.

Infection rates

During the index stay, 30 patients (3.7%) experienced an infection. Among patients with 30-day, 90-day, 1-year, and 2-years post-discharge follow-up data, infection rates were respectively: 8.0%, 9.2%, 11.7%, and 13.4% (Figure 2).

Figure 2. Cumulative percentage of infection events recorded post-index date

One-year inpatient costs

Among patients with index stay plus 1-year post discharge data (N=686), the mean 1-year total inpatient cost was significantly higher among patients who experienced an infection (£15,580;

n=80) compared with patients without infection (£7,746; p<0.001). After adjusting for fracture type (open/closed), age, smoking status, index year, diabetes, COPD, inpatient waiting time for surgery and compartment syndrome, mean costs were 80% (95% CI: 58%, 104%) higher, respectively (£13,672 [95% CI: £12,122, £15,420] versus £7,616 [95% CI: £7,301, £7,944]; p<0.001) (Figure 3).

One-year total costs

Adjusted total costs were £14,756 (95% CI: £13,123, £16,593) among patients who experienced an infection versus £8,279 (95% CI: £7,946, £8,626; p<0.001) in patients without infection – a 78% increase in total costs as a result of infection (95% CI: 57%, 102%) (Figure 3).

Figure 3. Breakdown of 1-year total costs by infection status (adjusted analysis)

Abbreviations: ns, not significant; CI, confidence interval.

*** p<0.001

One-year healthcare resource use

For the majority of healthcare resource categories, presence of infection was associated with a statistically significant increase in resource use versus no infection (Table 2). Key drivers of increased costs were LOS, readmission, and reoperation rates, which were all significantly higher in patients with infections (all p<0.001). After adjustment, LOS was increased by 109% (95% CI: 62%, 169%) from 10.5 days to 21.9 days. The odds of being readmitted or requiring reoperation due to infection was increased by 5.18 times (95% CI: 3.01, 9.13) and 2.47 times (95% CI: 1.48, 4.09), respectively.

Table 2. 1-year healthcare resource use by infection status

	Multivariate analysis		
	No infection (N=606) Mean (95% CI)	**Infection N=80 Mean (95% CI)**	**p-value**
LOS, days	10.5 (9.7, 11.4)	21.9 (17.3, 27.7)	p<0.001

	Multivariate analysis		
	No infection (N=606) Mean (95% CI)	**Infection N=80 Mean (95% CI)**	**p-value**
ICU LOS, days	0.01 (0.01, 0.02)	0.01 (0.00, 0.02)	p=0.91
Number of readmissions	0.5 (0.5, 0.6)	1.5 (1.2, 1.8)	p<0.001
Readmission rate, %	35.9 (32.1, 39.9)	74.4 (63.4, 83.0)	p<0.001
Number of reoperations	0.2 (0.2, 0.3)	0.6 (0.5, 0.8)	p<0.001
Reoperations rate, %	20.3 (17.2, 23.8)	38.6 (28.3, 50.0)	p<0.001
Number of hospital outpatient referrals	1.8 (1.6, 2.1)	1.7 (1.2, 2.1)	p=0.44
Primary care resource use			
Number of primary care events	30.9 (29.2, 32.7)	45.9 (39.0, 54.0)	p<0.001
Number of tests and examinations	14.0 (11.4, 16.6)	22.1 (13.9, 31.3)	p=0.052

Abbreviations: CI, confidence interval; ICU, intensive care unit; LOS, length of stay

Total costs from index stay to two years follow-up

At all time points mean total costs were statistically significantly higher for patients with an infection compared with those without (p<0.001) (Figure 4). Adjusted mean total costs of care in patients with infection versus no infection over time were: £11,257 versus £7,017 at 30 days; £11,949 versus £7,423 at 90 days; and £16,626 versus £9,439 at 2 years (all p<0.001).

Figure 4. Total costs from index stay to 2 years follow-up

Abbreviations: CI, confidence interval.

*** p<0.001. Data plotted are means +/- 95% CI.

Healthcare resource use from index stay to two years follow-up

Multivariate analysis demonstrated that LOS, readmissions (rate and mean; Figure 5), and reoperations (rate and mean; Figure 6), were consistently higher at all timepoints among patients who experienced an infection compared with those who did not (p<0.001). At 30 days, infection increased the adjusted LOS from 8.9 days to 15.0 days and at 2 years from 11.3 days to 24.6 days (both p<0.001). The adjusted readmission rate increased from 7.1% at 30 days to 51.3% at 2 years follow-up in patients without infection compared with an increase from 44.1%

to 77.6% in the infection group (Figure 5). The adjusted reoperation rate increased from 1.3% at 30 days to 31.2% at 2 years in the absence of infection, whereas in the infection group, the rate increased from 11.5% to 49.0% (Figure 6).

Figure 5. Readmission (adjusted) according to follow-up time: (A) readmission rate and (B) mean number of readmissions per patient

Abbreviations: CI, confidence interval.

*** p<0.001. Data plotted are means +/- 95% CI.

Figure 6. Reoperation (adjusted) according to follow-up time: (A) reoperation rate and (B) mean number of reoperations per patient

Abbreviations: CI, confidence interval.

** p<0.01, *** p<0.001. Data plotted are means +/- 95% CI.

Subgroup analyses

Multivariate analysis by infection type resulted in mean 1-year inpatient costs of £7,614, £12,814 and £15,513, respectively for no infection (n=606), superficial infection (n=54) and deep infection (n=26) (Additional file 2). Analysis by fracture type showed a higher 1-year infection rate among patients with open fractures (27.4%) versus closed fractures (8.6%). Mean adjusted inpatient costs at 1 year for patients with and without infection were £19,542 versus £9,495 for patients with open fractures and £12,178 versus £7,278 for patients with closed fractures.

Sensitivity analyses

A total of 588 patients (73%) out of the 805 patients at index had data for the full 2-year follow-up period. Results for total costs, LOS, readmissions (rate and mean), and reoperations (rate

and mean) at each time point were consistent with those of the primary analyses (Additional file 2).

Discussion

This study used CPRD-linked HES data to determine the impact of infection on English healthcare costs and resource utilisation associated with patients undergoing intramedullary nailing for tibial fracture. Infection rates at 1-year and 2-years (11.7% and 13.4%, respectively) were comparable with the 10.5% rate reported in a 2014 meta-analysis (6). Mean inpatient costs measured after 1 year were predicted to be 80% higher (£6,056) for patients with infection compared with those without infection, while overall costs were 78% higher. The greatest cost drivers were hospital LOS (109% increase at 1 year), readmissions (odds of being readmitted increased by 5.18 times at 1 year), and reoperations (odds of reoperation increased by 2.47 times at 1 year). The 2-year follow-up in this study meant that we were able to capture changes in resource use over time associated with infection, such as readmission and reoperation. The findings of this study highlight the substantial impact on healthcare resource utilisation and costs to the English NHS, from both the hospital and primary care perspective.

This study is the first to quantify the additional healthcare resource burden of infections following tibial fractures treated with intramedullary nailing in England with a long-term perspective which includes inpatient, hospital outpatient and primary care parameters. Differences in healthcare systems, patient populations and treatment pathways make direct comparison with studies from other countries challenging; however, our findings are in line with results of studies from Belgium and Denmark (11, 12). Hoekstra et al demonstrated five times higher healthcare costs and six times longer LOS for open tibial shaft fracture patients with deep infection versus those without infection in Belgium (11). Although the magnitude of the increase in costs and LOS observed in our study is not as substantial, differences in patient populations may be a contributing factor, as Hoekstra et al. did not limit their study population to intramedullary nail

fixation (11). In their Danish study, Olesen et al estimated a 60% increase in direct costs and an 80% increase in LOS resulting from infected open tibial fractures (12), consistent with the magnitude of the increase observed in the current study; absolute LOS (74 days) and direct healthcare costs (€81,155) in the presence of infection were substantially higher than in our study, however, which may in part reflect the most severe types of wounds considered in the Danish study, all of which were open fractures and 80% of which were Gustilo-Anderson classification 3.

This study is subject to the following limitations: 1) potential bias in the patient population as we only considered patients with complete follow-up, thus excluding very severe patients with short life expectancy; 2) identification of relevant patients for inclusion in the study was based on OPCS, ICD-10 and primary care-based read codes. The data may be susceptible to coding errors and misclassifications; 3) medication use was costed as recorded in CPRD , i.e. averaged to the cost of the drug family/British National Formulary sub-paragraph; 4) dispensing costs were not included 5) outpatient specialties from CPRD did not always exactly match outpatient specialty categories from NHS Reference Costs; when there was not an exact match, the closest matching specialty was chosen; 6) costs were not directly available from the CPRD dataset and hence unit costs had to be sourced from published national sources for primary and secondary care and for drug prices.

Our study provides important evidence as to the short- to mid-term direct economic consequences of infection following tibial fractures. By increasing the sample size, the impact of infection type (superficial/deep) and fracture type (open/closed) could have been explored more robustly. Additional validation of clinical codes used to identify relevant data would have allowed us to account for any potential variation in clinical coding practice. Broadening the perspective to include indirect costs would allow the additional burden of infection to be established, such as rehabilitation and absenteeism.

Conclusion

This study confirms that infection presents a substantial healthcare burden, leading to significantly increased hospital LOS, need for hospital readmission and reoperation, and increased use of GPs and other primary care resources. As such there exists an unmet need for alternative medical technologies and infection prevention strategies that could help to reduce infections in tibial shaft fractures and reduce costs. Our study indicates that the potential mid-term (1–2 years) saving to the English NHS of is around £6,500 per patient.

Declarations

Ethics approval and consent to participate

The study protocol was approved by the Independent Scientific Advisory Committee for Medicines and Healthcare products Regulatory Agency database research (ISAC) on 27 November 2017 (ISAC Protocol: 17-132R). General ethical approval for observational research using the CPRD with approval from the ISAC was granted by a Health Research Authority Research Ethics Committee (East Midlands – Derby; reference number: 05/MRE04/87).

Consent for publication

Not applicable

Availability of data and material

The data that support the findings of this study are available from Clinical Practice Research Datalink (CPRD) but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available.

Competing interests

Peter Giannoudis received honoraria from Synthes GmbH for his involvement in this study. Thibaut Galvain, Abhishek Chitnis, Cindy Tong, and Chantal Holy are employees of Johnson and Johnson. Konstantina Paparouni is an employee of Synthes GmbH.

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Authors' contributions

All authors contributed to the study design, data analysis, and manuscript writing.

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Abbreviations

CI, confidence interval; COPD, chronic obstructive pulmonary disease; CPRD, Clinical Practice Research Datalink; GP, general practitioner; HES, Hospital Episode Statistics; HRG, Healthcare Resource Group; ICU, intensive care unit; ISAC, Independent Scientific Advisory Committee; LOS, length of stay; NA, not applicable; NHS, National Health Service; SD, standard deviation.

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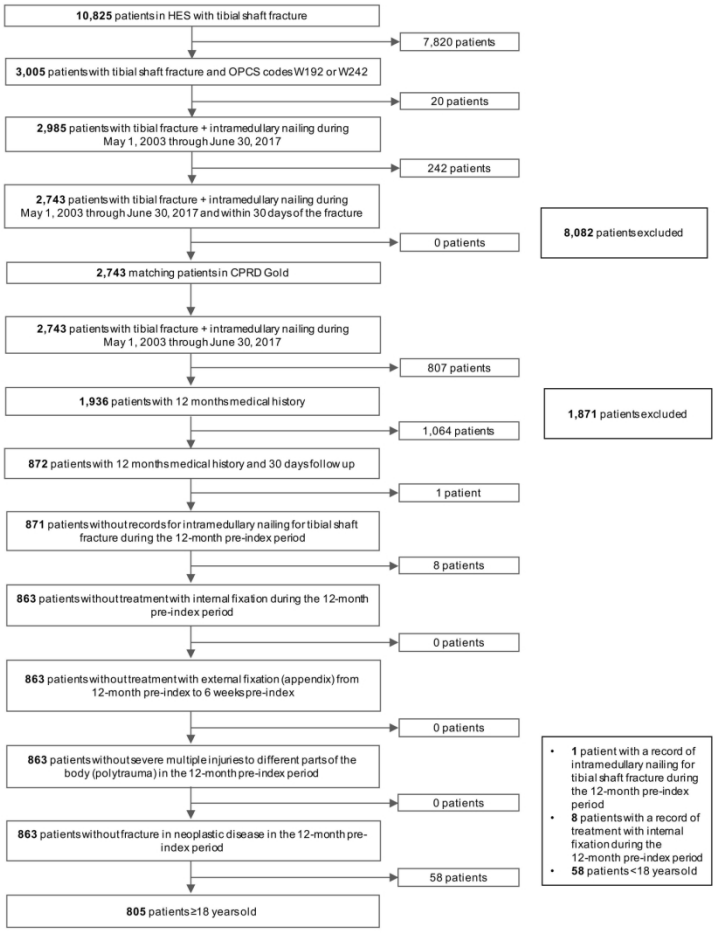
Additional files

1. Additional file 1:
    a. Format: “Additional file1.docx”
    b. Title: Study protocol
    c. Description: this additional file includes the study protocol and its appendix composed of clinical and procedure codes
2. Additional file 2:
    a. Format: “Additional file2.docx”

b. Title: Baseline and results at all time points

c. Description: this additional file includes the baseline demographics and results at all time points that could not be integrated in the manuscript.



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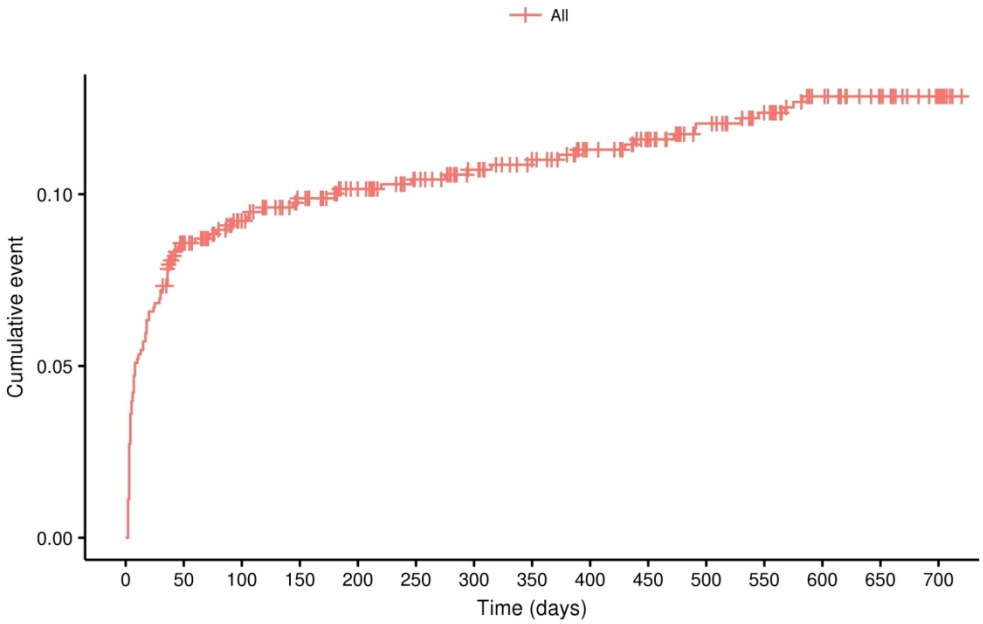

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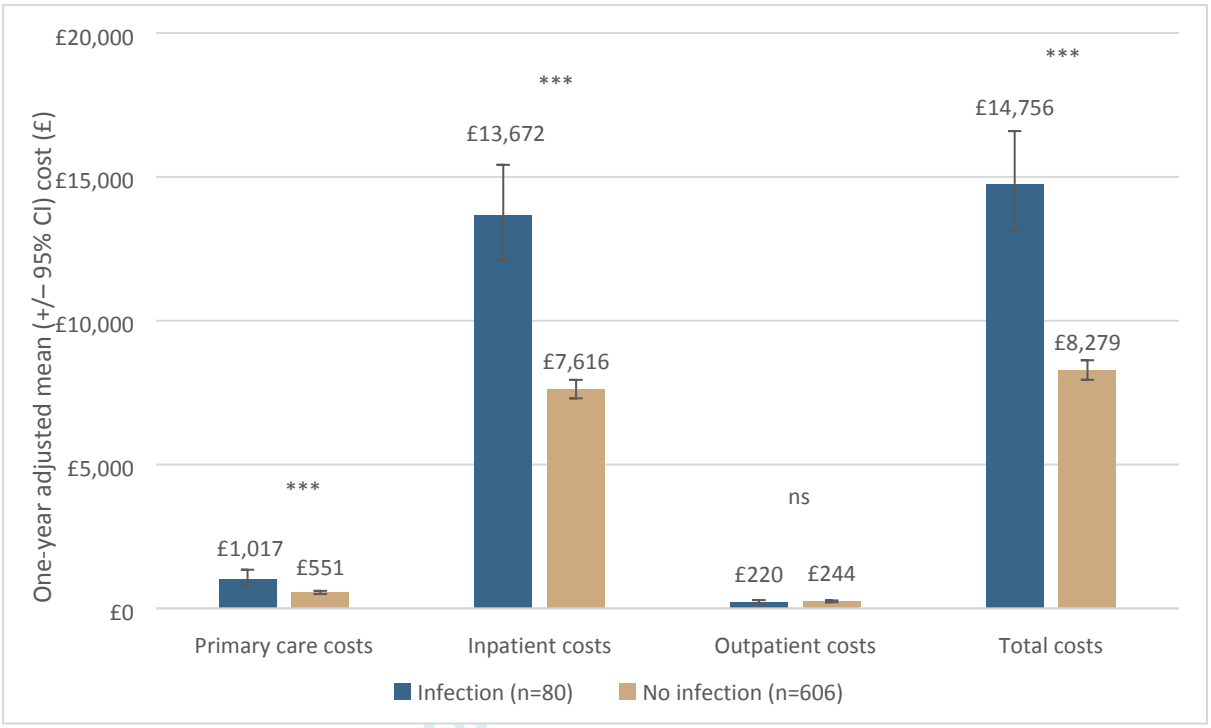
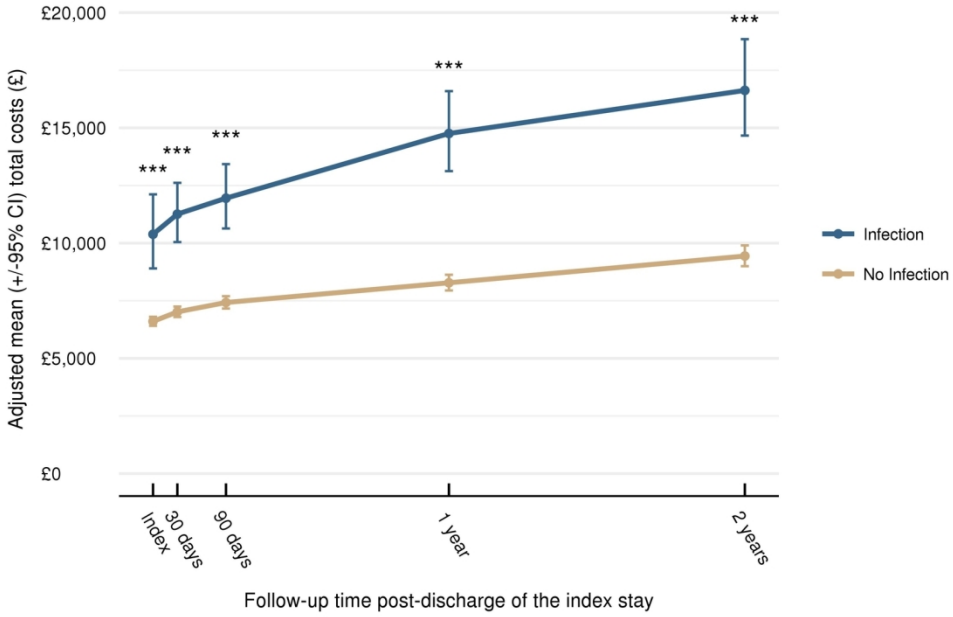




Abbreviations: CI, confidence interval. *** p<0.001. Data plotted are means +/- 95% CI.

152x101mm (300 x 300 DPI)

Figure 5A

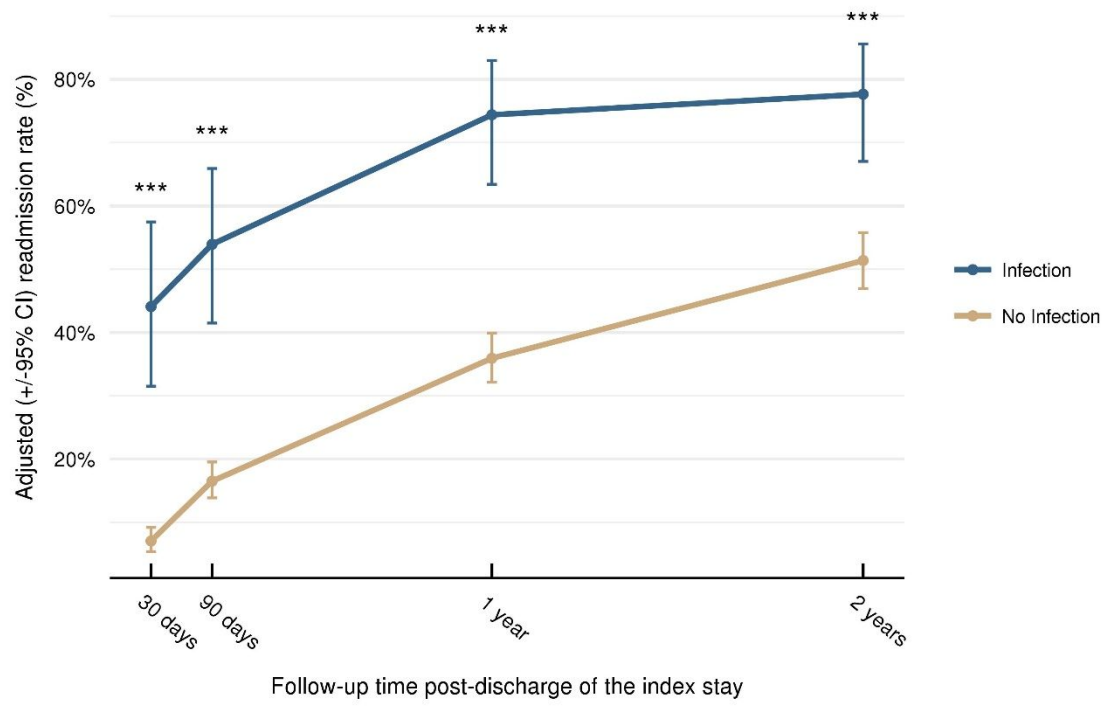


Figure 5B

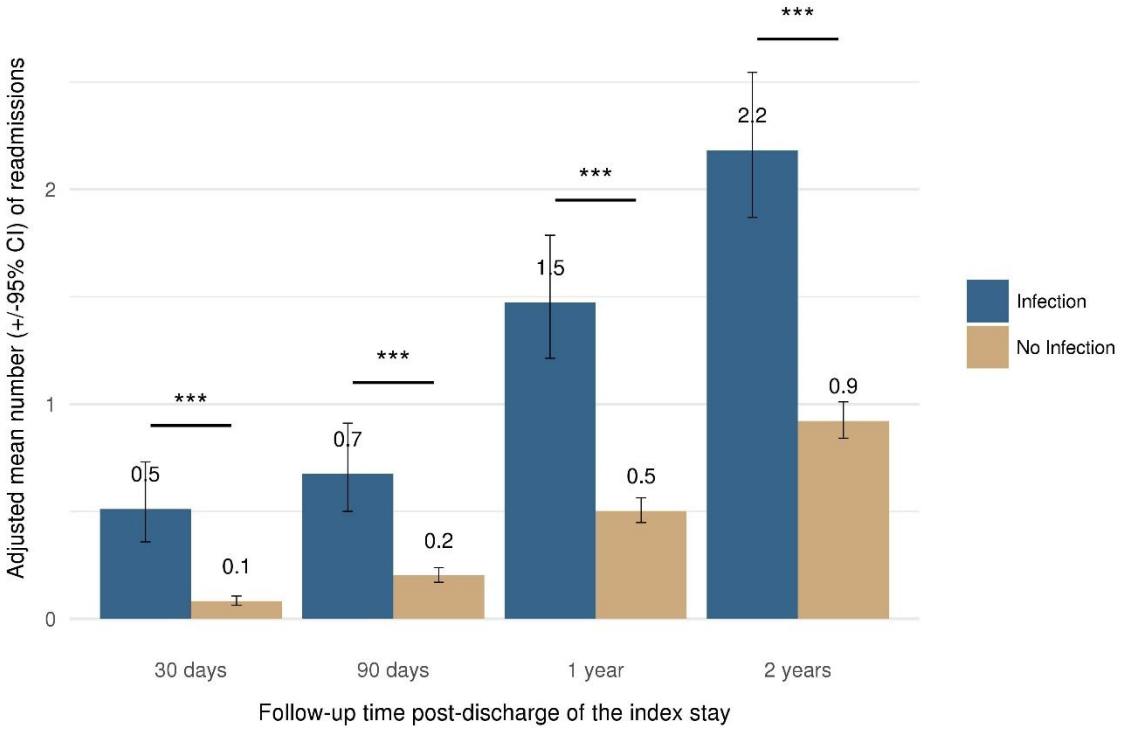


Figure 6A

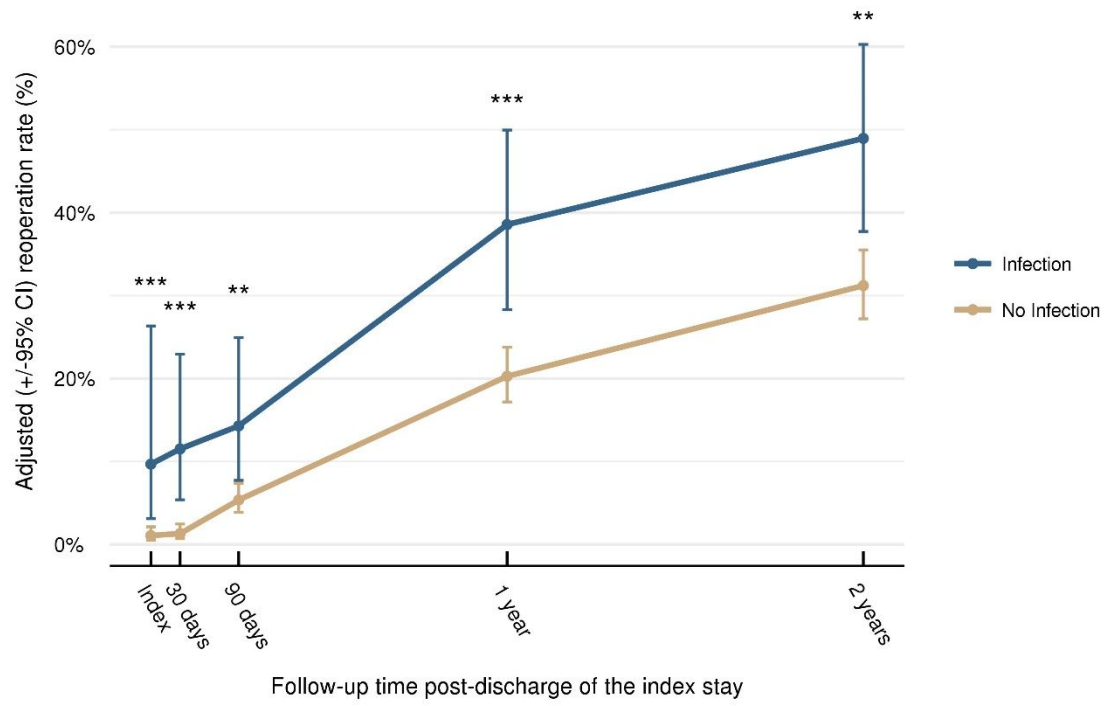
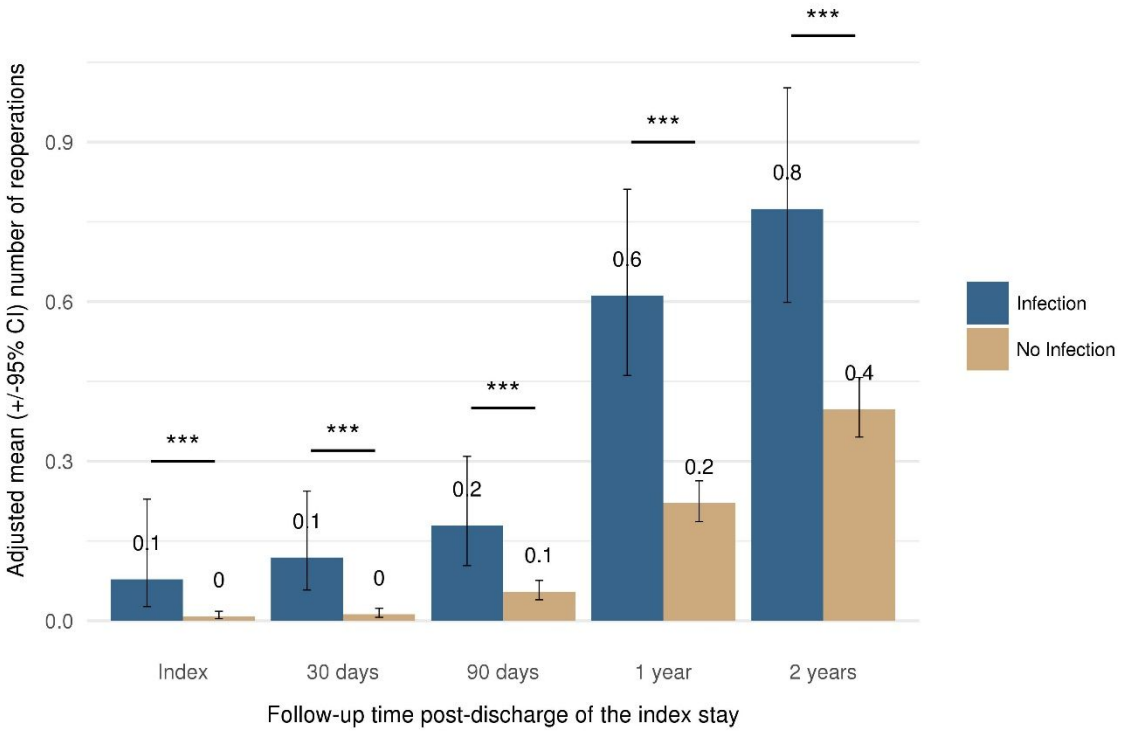


Figure 6B



Additional file 1: Study protocol

PROTOCOL INFORMATION REQUIRED

The following sections below **must** be included in the CPRD ISAC research protocol. Please refer to the guidance on '***Contents of CPRD ISAC Research Protocols***' (www.cprd.com/isac) for more information on how to complete the sections below. Pages should be numbered. All abbreviations must be defined on first use.

Applicants must complete all sections listed below
Sections which do not apply should be completed as '*Not Applicable*'

A. Study Title§

§Please note: This information will be published on CPRD's website as part of its transparency policy

Healthcare Resource Utilization and Costs among Patients with and without Infection after Intramedullary Nailing for A Tibial Shaft Fracture

B. Lay Summary (Max. 200 words)§

§Please note: This information will be published on CPRD's website as part of its transparency policy

Tibial shaft fractures are the most common long bone fracture of the lower limbs. Intramedullary nailing is the most frequent surgical treatment for tibial shaft fractures. In patients with tibial shaft fractures, infection is an important complication as about 15% of these fractures are open injuries. Such infections may lead to devastating consequences such as increase in length of hospital stay, readmissions, prolonged medication treatment and reoperations along with high use of medical resources and costs. However, the healthcare burden among patients developing an infection in tibial shaft fracture is not well documented. Consequently, this study seeks to understand the impact of infection after intramedullary nailing in patients with tibial shaft fractures on healthcare use and cost of care.

C. Technical Summary (Max. 200 words)§

§Please note: This information will be published on CPRD's website as part of its transparency policy

The objective of this retrospective longitudinal cohort study is primarily designed to determine short (30-day, 90-day) and mid-term (one-year, two-year) healthcare resource utilization (HRU) and costs among patients with deep and superficial infections versus those without following intramedullary nailing for a tibial shaft fracture. Patients with tibial shaft fracture treated with intramedullary nailing between 2011 and 2016 will be selected. The main exposure variable will include deep infection versus superficial surgical site infection or no infection. Analyses will be both descriptive and comparative using multivariable models. The multivariable models will include generalized linear models (GLMs) based on the outcome variable of interest for HRU and costs and will adjust for patient characteristics.

Applicants must complete all sections listed below
Sections which do not apply should be completed as *'Not Applicable'*

D. Objectives, Specific Aims and Rationale

Broad Research Objectives

To evaluate the impact of developing infection in patients with intramedullary nailing for tibial shaft fractures on healthcare utilization and cost of care.

Specific Aims

1. To determine short (30-day, 90-day) and mid-term (one-year, two-year) Costs and HRU among patients with deep infection and superficial infections versus patients without an infection following tibial shaft fracture treated with nailing.

Rationale

This study seeks to understand the impact of post-surgical infection in patients with intramedullary nailing for tibial shaft fractures on cost of care and healthcare utilization.

E. Study Background

Infections remains a feared complication in orthopaedic and trauma surgery due to its potentially devastating consequences for patients. It has also been associated with an increase in medical resource utilization and treatment costs due to increased length of hospital stay, readmissions, prolonged pharmacological treatment and reoperations. [1-6] Deep infections defined as infections involving deeper tissues such as muscular fascia and bone[7] have been associated with a significant economic burden for healthcare systems. Data from long bone fracture reduction, hip replacement or hemiarthroplasty or screw fixation for proximal humeral fractures and knee arthroplasty, consistently reported 2-3 times higher treatment costs for patients that developed an infection compared to those that did not. [1-6]

Tibial shaft fractures are the most common long bone fracture of the lower limbs.[8] In patients with tibial shaft fractures, infection is an important complication as about 15% of these fractures are open injuries. Infection may lead to prolonged treatment, compromised clinical outcomes and in some cases, even limb amputation. [9-12] In the European setting there is limited data available with respect to the actual cost of treatment. In a Danish study on patients with open tibia fractures treated with a free flap , the presence of an infection increased the mean length of hospital stay from 28 to 63.8 days and the mean treatment costs from €49,301 to €67,958 for infected compared to uninfected fractures.[13]A study from the UK reported the mean length of stay and treatment costs of patients with tibial osteomyelitis. For patients treated with limb salvage procedures alone, length of stay was 15 days (10-27) and corresponding treatment costs were € 16,718 while for patients, whose treatment ended up in amputation length of stay was 13 days (8-17) and treatment costs were €18,441.[14]

Intramedullary nailing is the preferred surgical treatment in patients with tibial shaft fractures. The impact of the development of an infection on short and mid-term post-operative medical resource utilization is not well documented. While literature from clinical trials provides some insight into infection incidence rates, the treatment pathway and treatment success/failure rates, there is a lack of detailed patient-level information particularly in relation to the actual costs of care.

Applicants must complete all sections listed below
Sections which do not apply should be completed as '*Not Applicable*'

F. Study Type

Hypothesis generating

This study will generate the hypothesis for HRU and costs between patients with (deep and superficial) and without infection after intramedullary nailing for tibial shaft fractures

G. Study Design

This is a retrospective cohort study with a longitudinal follow-up for up to two years post intramedullary nailing for tibial shaft fractures.

H. Feasibility counts

Based on the preliminary feasibility study of Hospital Episode Statistics (HES) inpatient data for research grade patients with complete data, we identified a total of 11,329 patients with intramedullary nailing for a tibial shaft fracture between 2011 and 2013 of which 509 patients had an infection following intramedullary nailing for a tibial shaft fracture.

I. Sample size considerations

No prior real-world studies have been conducted to evaluate the health care resource use and costs of interest among patients with and without infection following intramedullary nailing for tibial shaft fracture. Therefore, it is not possible to estimate the sample size

J. Data Linkage Required (if applicable):§

§Please note that the data linkage/s requested in research protocols will be published by the CPRD as part of its transparency policy

The Clinical Practice Research Datalink (CPRD) with HES is required to identify the patients and outcomes that are based on diagnosis and procedures recorded in the inpatient setting.

K. Study population

Patients initially selected for tibial shaft fracture (ICD-10, S822) must meet all the following inclusion criteria:

1. Procedure for intramedullary nailing for tibial shaft fracture (appendix) between January 1, 2011 and February 30, 2016
   - Date of first intramedullary nailing for tibial shaft fracture between January 2011 and February 2016 will be the index date
2. Research grade patients with complete medical records for at least 12 months pre- and 30- day post index date. Patients with 90-day, 1- and 2- year follow-up or continuous enrollment will be further analysed.

Patients with the following criteria were excluded:

1. Records for intramedullary nailing for tibial shaft fracture during the 12-month pre-index period
2. Records for treatment with internal fixation (appendix) during the 12-month pre-index period

Applicants must complete all sections listed below
Sections which do not apply should be completed as '*Not Applicable*'

3. Records for treatment with external fixation (appendix) from 12-month pre-index to 6 weeks pre-index. Records for external fixation during 6 weeks pre-index will be included as external fixation is often performed prior to intramedullary nailing.
4. Records for severe multiple injuries to different parts of the body (polytrauma) (appendix) in the 12-month pre-index period.
5. Records for a fracture in neoplastic disease (appendix) in the 12-month pre-index period.

L. Selection of comparison group(s) or controls

Patients not developing an infection anytime during the study period will be selected as the control group.

M. Exposures, Health Outcomes§ and Covariates

§Please note: Summary information on health outcomes (as included on the ISAC application form above)will be published on CPRD's website as part of its transparency policy

Exposure

Patients developing infection during the 12-month post index period.

Outcome(s)

Primary Outcome

One- year inpatient costs

Secondary Outcomes

- Number of hospital readmissions (in 30-days, 90-days, 1 year and 2 years)
- Percent (yes/no) of patients with readmissions (in 30-days, 90-days, 1 year and 2 years)
- Total cost of care at the different time points (in 30-days, 90-days, 1 year and 2 years)
    a. Inpatient admissions
    b. Outpatient costs
    c. Pharmacy

Costs will be expressed in UK pounds and adjusted for inflation to 2015 index. Healthcare costs will be obtained from the Personal Social Services Research Unit (PSSRU) 2015 Cost of Care public document and Healthcare Resource Group (HRG) codes available in HES. Drug costs will be obtained from British National Formulary 71 (March 2016-September 2016).

- Number of procedures for introduction of therapeutic substance (Appendix) (30-days, 90-days, 1 year and 2 years)
- Number of outpatient visits (all-cause) at the different time points (in 30-days, 90-days, 1 year and 2 years)
- Number of diagnostic tests and imaging (all-cause) at the different time points (in 30-days, 90-days, 1 year and 2 years)
- Number of days in ICU (all-cause) at the different time points (in 30-days, 90-days, 1 year and 2 years)
- Time of infection and type of infection (bacterial vs other)

Applicants must complete all sections listed below
Sections which do not apply should be completed as '*Not Applicable*'

- Percent (yes/no) of patients with use of antibiotics at the different time points (in 30-days, 90-days, 1 year and 2 years)
- Patients necessitated amputation (Appendix) at the different time points (in 30-days, 90-days, 1 year and 2 years)

Covariates

The covariates information will be captured during 12-month pre-index period and will include the following:

Patient Demographics

- Age
- Gender
- Smoking status

Procedural Characteristics

- Year of the index date

Patient Clinical Characteristics

Comorbidities (Appendix)

- Diabetes
- Dyspnea
- Ventilator requirement
- Chronic obstructive pulmonary disease (COPD)
- Congestive heart failure (CHF)
- Renal failure
- Hypertension

Indices

- Charlson comorbidity index (CCI) - The CCI is an aggregate measure of comorbidity created by using select diagnoses associated with chronic disease (e.g., heart disease, cancer). The CCI includes 17 medical conditions and weights these conditions from +1 to +6.

Medications

- Anti-hypertensive medications
- Opioids

N. Data/ Statistical Analysis

All study variables will be analyzed descriptively. Frequency counts and proportions will be provided for dichotomous and polychotomous variables. Means, medians, and standard deviations will be provided for continuous variables. Time to infection will be depicted graphically using Kaplan-Meier curve.

Unadjusted comparisons of patient demographics, comorbidities and medication use between groups (with and without infection) will be performed with 2-sample t-tests for continuous variables and $\chi 2$ tests for categorical variables and Wilcoxon rank sum tests for cost variables.

Applicants must complete all sections listed below Sections which do not apply should be completed as '*Not Applicable*'
A sub-analysis will be conducted in which patients will be stratified by an open fracture and a closed tibial shaft fracture (appendix) to determine the outcomes. All analyses will be conducted using SAS for Windows. Statistical significance will be set a-priori at p< 0.05 (two-sided). In addition, a generalized Linear Model (GLM) will be utilized to get adjusted results after control for confounding. Details of this methods are mentioned in the section below:
O. Plan for addressing confounding Multivariable models will be constructed to examine the impact of infection versus no infection and other patient characteristics for healthcare utilization and cost outcomes. A Generalized Linear Model (GLM) will be utilized and the appropriate error distribution and link function will be used based on the outcome variable of interest for utilization and costs. Following standard procedures, for each model regression diagnostics will be performed to assess goodness of fit and violations of model assumptions. Appropriate modifications will be made as needed either through selection of alternative error distributions or link functions, or through transformations of either the independent or dependent variables. We will also examine the fitted and the observed data to uncover outliers, their effect on the analysis, and possible misspecification of the initial equation.
P. Plans for addressing missing data Missing data will not be imputed for the analyses. Most variables (drugs, procedures, diagnosis) can have no missing values, as they are assumed not to have occurred unless a record is identified. To be included in the study, patients will need to have complete medical history for at least 12 months pre-index to 12 months post-index date.
Q. Patient or user group involvement (if applicable) This is purely an observational study using CPRD with HES linkage data. This study does not involve requesting additional information from GPs. Also, the study does not require contacting patients to get any additional information.
R. Plans for disseminating and communicating study results, including the presence or absence of any restrictions on the extent and timing of publication The study will be disseminated per the ICMJE guidelines. We plan on submitting the results to a peer-reviewed journal and presenting the results at scientific conferences.
S. Limitations of the study design, data sources, and analytic methods

Applicants must complete all sections listed below
Sections which do not apply should be completed as *'Not Applicable'*

- Potential bias in patient population: only patients with complete medical history for 12 months post index will be included, thus excluding very severe patients with less than 12 month life expectancy
- Coding errors and misclassifications
- Under-reported or missing diagnoses, based on patients' choice (not to seek care) or access challenges
- Identify pharmacy cost in terms of medication prescribed in the primary care setting only
- Cost evaluated using PSSRU, HRG and BNF codes as the costs are not directly available in the data

T. References

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12. Mouzopoulos G, Kanakaris NK, Kontakis G, et al. Management of bone infections in adults: the surgeon's and microbiologist's perspectives. Injury 2011;**42 Suppl 5**:S18-23.
13. The cost of infection in severe open tibial fractures treated with a free flap. 34th Annual Meeting of the European Bone & Joint Infection Society; 2015; Lisbon, Portugal.
14. Kendall J, Jones, S., Mcnally, M. Income and costs of treating tibial osteomyelitis in the uk – a comparison of limb salvage versus amputation. 34th Annual Meeting of the European Bone & Joint Infection Society. Lisbon, Portugal, 2015.

List of Appendices *(Submit all appendices as separate documents to this application)*

Applicants must complete all sections listed below
Sections which do not apply should be completed as '*Not Applicable*'

Appendix 1: OPCS-4 codes to identify intramedullary nailing for long bones
Appendix 2 OPCS-4 codes to identify internal fixation
Appendix 3 OPCS-4 codes to identify external fixation
Appendix 4: ICD-10 codes to identify severe multiple injuries
Appendix 5: Read codes to identify fracture due to neoplastic disease
Appendix 6: ICD-10, OPCS and Read codes to identify infection
Appendix 7: OPCS-4 codes to identify procedures for introduction of therapeutic substance
Appendix 8: OPCS-4 codes to identify procedures amputation of tibia bone
Appendix 9: Read codes to identify diabetes mellitus with and without complications
Appendix 10: Read codes to identify dyspnoea
Appendix 11: Read codes to identify ventilator requirement
Appendix 12: Read codes to identify COPD
Appendix 13: Read codes to identify heart failure
Appendix 14: Read codes to identify renal failure
Appendix 15: Read codes to identify hypertension
Appendix 16: Read, ICD-10 and OPCS codes to identify open and closed tibial shaft fracture
Appendix 17: Read codes to identify Charlson comorbidity index
Appendix 18: OPCS codes to identify reoperations

1. OPCS-4 codes to identify intramedullary nailing for long bones

OPCS-4	Description
W192	Primary open reduction of fracture of long bone and fixation using rigid nail NEC
W242	Closed reduction of fracture of long bone and rigid internal fixation NEC

2. OPCS-4 codes to identify internal fixation

OPCS-4	Description
O172	Remanipulation of fracture of long bone and rigid internal fixation NEC
O173	Remanipulation of fracture of long bone and flexible internal fixation HFQ
O175	Remanipulation of fragment of bone and fixation using screw
O178	Other specified secondary closed reduction of fracture of bone and internal fixation
O179	Unspecified secondary closed reduction of fracture of bone and internal fixation
W195	Primary open reduction of fragment of bone and fixation using screw
W196	Primary open reduction of fragment of bone and fixation using wire system
W198	Other specified primary open reduction of fracture of bone and intramedullary fixation
W199	Unspecified primary open reduction of fracture of bone and intramedullary fixation

OPCS-4	Description
W201	Primary open reduction of fracture of long bone and extramedullary fixation using plate NEC
W202	Primary open reduction of fracture of long bone and extramedullary fixation using cerclage
W203	Primary open reduction of fracture of long bone and extramedullary fixation using suture
W204	Primary open reduction of fracture of long bone and complex extramedullary fixation NEC
W208	Other specified primary open reduction of fracture of bone and extramedullary fixation
W209	Unspecified primary open reduction of fracture of bone and extramedullary fixation
W231	Secondary open reduction of fracture of bone and intramedullary fixation HFQ
W232	Secondary open reduction of fracture of bone and extramedullary fixation HFQ
W236	Secondary open reduction of fracture of bone and internal fixation HFQ
W248	Other specified closed reduction of fracture of bone and internal fixation
W249	Unspecified closed reduction of fracture of bone and internal fixation
W281	Application of internal fixation to bone NEC
W282	Adjustment to internal fixation of bone NEC
W283	Removal of internal fixation from bone NEC
W288	Other specified other internal fixation of bone
W289	Unspecified other internal fixation of bone

3. OPCS-4 codes to identify external fixation

OPCS-4	Description
W222	Primary open reduction of fracture of bone and external fixation HFQ
W235	Secondary open reduction of fracture of bone and external fixation HFQ
W252	Closed reduction of fracture of bone and fixation using functional bracing system
W253	Remanipulation of fracture of bone and external fixation HFQ
W258	Other specified closed reduction of fracture of bone and external fixation
W259	Unspecified closed reduction of fracture of bone and external fixation
W301	Application of external fixation to bone NEC
W302	Adjustment to external fixation of bone NEC
W303	Removal of external fixation from bone NEC
W304	Application of external ring fixation to bone NEC
W308	Other specified other external fixation of bone
W309	Unspecified other external fixation of bone

4. ICD-10 codes to identify severe multiple injuries

ICD-10 codes	Description
S097	Multiple injuries of head
S197	Multiple injuries of neck
S277	Multiple injuries of intrathoracic organs
S297	Multiple injuries of thorax
S397	Other multiple injuries of abdomen, lower back and pelvis
S497	Multiple injuries of shoulder and upper arm
S597	Multiple injuries of forearm
S647	Injury of multiple nerves at wrist and hand level
S697	Multiple injuries of wrist and hand
S797	Multiple injuries of hip and thigh
S897	Multiple injuries of lower leg
S997	Multiple injuries of ankle and foot
T042	Crushing injuries involving multiple region of upper limb(s)
T043	Crushing injuries involving multiple region of lower limb(s)
T062	Injuries of nerves involving multiple body regions
T063	Injuries of blood vessels involving multiple body regions
T068	Other specified injuries involving multiple body regions
T07X	Unspecified multiple injuries

5. Read codes to identify fracture due to neoplastic disease

Medcode	Read_code	Description
54834	N331700	Fracture of bone in neoplastic disease

6. ICD-10, OPCS and Read codes to identify infection

ICD-10 codes	Description	Deep/Superficial
A498	Other bacterial infections of unspecified site	Deep
A499	Bacterial infection, unspecified	Deep
A544	Gonococcal infection of musculoskeletal system	Deep
L088	Other spec local infections of skin and subcutaneous tissue	Superficial
L089	Local infection of skin and subcutaneous tissue, unspecified	Superficial
T814	Infection following a procedure, not elsewhere classified	Deep

Medcode	Read_code	Description	Deep/Superficial
3128	M07z.00	Local infection skin/subcut tissue NOS	Superficial
6956	SK03.00	Post-traumatic wound infection NEC	Deep
7155	N302.11	Bone infection	Deep
51854	SP25600	Postoperative wound infection-deep	Deep
20342	N30..00	Osteomyelitis, periostitis, other infections affecting bone	Deep
21073	M07y.00	Local infection of skin or subcutaneous tissue OS	Superficial
25363	SP06800	Infection and inflamm reac due inter ortho device	Deep
40293	SP06.00	Infection and inflammation due to internal prosthetic device	Deep
30381	SP05612	[X]Prosthetic infection	Deep
33381	A3Byz00	Other specified bacterial infection NOS	Superficial
43058	N30z.00	Bone infection NOS	Deep
39830	N300.12	Acute bone infection	Deep
40293	SP06.00	Infection and inflammation due to internal prosthetic device	Deep
52122	Myu0.00	[X]Infections of the skin and subcutaneous tissue	Superficial
69280	N30z600	Bone infection NOS, of the lower leg	Deep
69855	N30y600	Other infections involving bone, of the lower leg	Deep
4207	M03z000	Cellulitis NOS	Superficial

OPCS-4	Description	Deep/Superficial
S571	Debridement of skin NEC	Superficial
W332	Debridement of open fracture of bone	Deep
T963	Debridement of soft tissue NEC	Deep
W336	Debridement of bone NEC	Deep

7. OPCS-4 codes to identify procedures for debridement or introduction of therapeutic substance

OPCS-4	Description
S571	Debridement of skin NEC
W332	Debridement of open fracture of bone
T963	Debridement of soft tissue NEC

W336	Debridement of bone NEC
W283	Removal of internal fixation from bone NEC
X292	Continuous intravenous infusion of therapeutic substance NEC
S523	Insertion of therapeutic substance into subcutaneous tissue NEC
W351	Introduction of therapeutic substance into bone

8. OPCS-4 codes to identify procedures amputation of tibia bone

OPCS-4	Description
X094	Amputation of leg through knee
X095	Amputation of leg below knee
X098	Other specified amputation of leg
X099	Unspecified amputation of leg

9. Read codes to identify diabetes mellitus with and without complications

Medcodes	Read code	Description
231370	66AJ.11	Unstable diabetes
297735	C108600	Insulin dependent diabetes mellitus with gangrene
288454	C101100	Diabetes mellitus, adult onset, with ketoacidosis
344495	C10M.00	Lipoatrophic diabetes mellitus
224500	C103000	Diabetes mellitus, juvenile type, with ketoacidotic coma
233608	C109500	Non-insulin dependent diabetes mellitus with gangrene
251808	C109900	Non-insulin-dependent diabetes mellitus without complication
331810	C109412	Type 2 diabetes mellitus with ulcer
344028	C10FG00	Type 2 diabetes mellitus with arthropathy
279344	C109.11	NIDDM - Non-insulin dependent diabetes mellitus
343531	C109G11	Type II diabetes mellitus with arthropathy
279348	C10z.00	Diabetes mellitus with unspecified complication
342740	C10EM11	Type I diabetes mellitus with ketoacidosis
279343	C107200	Diabetes mellitus, adult with gangrene
210870	250 GA	Gangrene diabetic
339961	C10FJ00	Insulin treated Type 2 diabetes mellitus
308067	C108911	Type I diabetes mellitus maturity onset
297727	C102z00	Diabetes mellitus NOS with hyperosmolar coma
283820	250 HC	Hypoglycaemic Coma Diabetic
303253	250 AK	Maturity Onset Diabetes Mellitus Insulin
243302	G73y000	Diabetic Peripheral Angiopathy

Medcodes	Read code	Description
306131	250 E	Hypoglycaemia In Diabetes Mellitus
249566	66AJ.00	Diabetic - Poor Control
331925	C109J12	Insulin treated Type II diabetes mellitus
309010	C109F12	Type 2 diabetes mellitus with peripheral angiopathy
242649	C109300	Non-insulin-dependent diabetes mellitus with multiple comps
242646	C108400	Unstable insulin dependent diabetes mellitus
340367	C10F900	Type 2 diabetes mellitus without complication
206461	C10y.00	Diabetes mellitus with other specified manifestation
344412	C10F.11	Type II diabetes mellitus
341116	C10FL00	Type 2 diabetes mellitus with persistent proteinuria
306134	250 NT	UNSTABLE DIABETIC
309704	C109G00	Non-insulin dependent diabetes mellitus with arthropathy
343565	C109G12	Type 2 diabetes mellitus with arthropathy
249564	66A5.00	Diabetic on insulin
308094	C109511	Type II diabetes mellitus with gangrene
243795	L180600	Pre-existing diabetes mellitus, non-insulin-dependent
256384	250 PR	Pruritus Diabetic
341003	C10FN00	Type 2 diabetes mellitus with ketoacidosis
341356	C10E400	Unstable type 1 diabetes mellitus
270277	C10zy00	Other specified diabetes mellitus with unspecified comps
341680	C10D.00	Diabetes mellitus autosomal dominant type 2
288459	C107z00	Diabetes mellitus NOS with peripheral circulatory disorder
341002	C10EN00	Type 1 diabetes mellitus with ketoacidotic coma
303258	250 CT	Diabetic Cataract
215438	C101000	Diabetes mellitus, juvenile type, with ketoacidosis
206451	C100011	Insulin dependent diabetes mellitus
229069	250 JA	Diabetic Acidosis
309863	C108411	Unstable type I diabetes mellitus
303250	250 A	Sugar Diabetes
206452	C103.00	Diabetes mellitus with ketoacidotic coma
261004	C107.11	Diabetes mellitus with gangrene
303263	250 JL	Ketosis Diabetic
303256	250 AN	Diabetes
341598	C10E500	Type 1 diabetes mellitus with ulcer

Medcodes	Read code	Description
242650	C109400	Non-insulin dependent diabetes mellitus with ulcer
297739	C10yy00	Other specified diabetes mellitus with other spec comps
292948	250 AB	Abscess Diabetic
307957	C109711	Type II diabetes mellitus - poor control
261009	C10A000	Malnutrition-related diabetes mellitus with coma
339633	C10F.00	Type 2 diabetes mellitus
309658	C109J11	Insulin treated non-insulin dependent diabetes mellitus
223592	8A13.00	Diabetic stabilisation
233607	C108.00	Insulin dependent diabetes mellitus
347683	C10EG00	Type 1 diabetes mellitus with peripheral angiopathy
340865	C108E12	Type 1 diabetes mellitus with hypoglycaemic coma
302787	C108.13	Type I diabetes mellitus
270271	C107100	Diabetes mellitus, adult, peripheral circulatory disorder
233609	C10A100	Malnutrition-related diabetes mellitus with ketoacidosis
261001	C102000	Diabetes mellitus, juvenile type, with hyperosmolar coma
237987	250 AT	Diabetic Amyotrophy
308119	C109411	Type II diabetes mellitus with ulcer
341509	C10F500	Type 2 diabetes mellitus with gangrene
303262	250 JK	Ketoacidosis Diabetic
297726	C102100	Diabetes mellitus, adult onset, with hyperosmolar coma
308004	C108E11	Type I diabetes mellitus with hypoglycaemic coma
339527	C109K00	Hyperosmolar non-ketotic state in type 2 diabetes mellitus
247153	250 G	Ulcer Diabetic
258769	66AJz00	Diabetic - poor control NOS
347258	C10FJ11	Insulin treated Type II diabetes mellitus
297734	C108500	Insulin dependent diabetes mellitus with ulcer
309300	C109J00	Insulin treated Type 2 diabetes mellitus
341126	C10E800	Type 1 diabetes mellitus - poor control
309125	C108812	Type 1 diabetes mellitus - poor control
206454	C107400	NIDDM with peripheral circulatory disorder
343055	C10G.00	Secondary pancreatic diabetes mellitus
340580	C10EM00	Type 1 diabetes mellitus with ketoacidosis
331540	66AV.00	Diabetic on insulin and oral treatment
298869	L180500	Pre-existing diabetes mellitus, insulin-dependent

Medcodes	Read code	Description
342313	C10FP00	Type 2 diabetes mellitus with ketoacidotic coma
297725	C100.00	Diabetes mellitus with no mention of complication
344338	C10E600	Type 1 diabetes mellitus with gangrene
333576	C109D12	Type 2 diabetes mellitus with hypoglycaemic coma
341127	C10FF00	Type 2 diabetes mellitus with peripheral angiopathy
261005	C108.12	Type 1 diabetes mellitus
206457	C109.00	Non-insulin-dependent diabetes mellitus
331823	C109D00	Non-insulin dependent diabetes mellitus with hypoglyca coma
242656	C10zz00	Diabetes mellitus NOS with unspecified complication
340814	C10EE00	Type 1 diabetes mellitus with hypoglycaemic coma
295382	66AS.00	Diabetic annual review
233606	C107000	Diabetes mellitus, juvenile ??? circulatory disorder
347648	C10E412	Unstable insulin dependent diabetes mellitus
341139	C10E900	Type 1 diabetes mellitus maturity onset
242642	C101y00	Other specified diabetes mellitus with ketoacidosis
344989	C10FL11	Type II diabetes mellitus with persistent proteinuria
247152	250 DR	Diabetic Diarrhoea
283822	250 NH	Hyperosmolar Diabetic State
303259	250 DC	Dietary Control Diabetes
310005	C109712	Type 2 diabetes mellitus - poor control
270372	Cyu2.00	[X]Diabetes mellitus
270268	C10..00	Diabetes mellitus
346131	C10EA00	Type 1 diabetes mellitus without complication
279341	C100z00	Diabetes mellitus NOS with no mention of complication
297729	C103z00	Diabetes mellitus NOS with ketoacidotic coma
331809	C108G00	Insulin dependent diab mell with peripheral angiopathy
308089	C108E00	Insulin dependent diabetes mellitus with hypoglycaemic coma
215437	C101.00	Diabetes mellitus with ketoacidosis
347882	C10E812	Insulin dependent diabetes mellitus - poor control
341302	C10F700	Type 2 diabetes mellitus - poor control
222266	66AK.00	Diabetic - cooperative patient
270276	C10B000	Steroid induced diabetes mellitus without complication
233603	C100111	Maturity onset diabetes
339632	C10E.00	Type 1 diabetes mellitus

Medcodes	Read code	Description
223655	8H2J.00	Admit diabetic emergency
283823	2500AH	Latent Diabetes
285267	1434	H/O: diabetes mellitus
308820	C108811	Type I diabetes mellitus - poor control
344076	C10E.12	Insulin dependent diabetes mellitus
270269	C100100	Diabetes mellitus, adult onset, no mention of complication
341357	C10F400	Type 2 diabetes mellitus with ulcer
242655	C10z100	Diabetes mellitus, adult onset, unspecified complication
280482	L180X00	Pre-existing diabetes mellitus, unspecified
341557	8BL2.00	Patient on maximal tolerated therapy for diabetes
242653	C10yz00	Diabetes mellitus NOS with other specified manifestation
288455	C102.00	Diabetes mellitus with hyperosmolar coma
270275	C10A.00	Malnutrition-related diabetes mellitus
270273	C108.11	IDDM-Insulin dependent diabetes mellitus
215439	C101z00	Diabetes mellitus NOS with ketoacidosis
342317	C10FD00	Type 2 diabetes mellitus with hypoglycaemic coma
261007	C108800	Insulin dependent diabetes mellitus - poor control
303261	250 HP	Precoma Diabetic
341856	C10EK00	Type 1 diabetes mellitus with persistent proteinuria
303252	250 AD	Diabetes Mellitus Insulin Dependant
347025	C10H.00	Diabetes mellitus induced by non-steroid drugs
270270	C107.00	Diabetes mellitus with peripheral circulatory disorder
332066	C10D.11	Maturity onset diabetes in youth type 2
224506	C107300	IDDM with peripheral circulatory disorder
340332	C109F11	Type II diabetes mellitus with peripheral angiopathy
309143	C109D11	Type II diabetes mellitus with hypoglycaemic coma
341409	C10EL00	Type 1 diabetes mellitus with persistent microalbuminuria
242641	C100112	Non-insulin dependent diabetes mellitus
340474	C10FM00	Type 2 diabetes mellitus with persistent microalbuminuria
261095	Cyu2000	[X]Other specified diabetes mellitus
288460	C109.12	Type 2 diabetes mellitus
224501	C103y00	Other specified diabetes mellitus with coma
302788	C109.13	Type II diabetes mellitus
332948	C108511	Type I diabetes mellitus with ulcer

Medcodes	Read code	Description
347834	C10EN11	Type I diabetes mellitus with ketoacidotic coma
297738	C109700	Non-insulin dependent diabetes mellitus - poor control
283819	250 H	Coma Diabetic
215444	C10y100	Diabetes mellitus, adult, other specified manifestation
346130	C10E.11	Type I diabetes mellitus
344745	C10N.00	Secondary diabetes mellitus
347629	C10F711	Type II diabetes mellitus - poor control
277055	66AI.00	Diabetic - good control
251805	C100000	Diabetes mellitus, juvenile type, no mention of complication
206900	F464000	Diabetic cataract
309738	C109212	Type 2 diabetes mellitus with neurological complications
224502	C104000	Diabetes mellitus, juvenile type, with renal manifestation
345097	C109111	Type II diabetes mellitus with ophthalmic complications
341813	2BBP.00	O/E - right eye background diabetic retinopathy
346841	C108C11	Type I diabetes mellitus with polyneuropathy
308934	C108H00	Insulin dependent diabetes mellitus with arthropathy
215442	C109C00	Non-insulin dependent diabetes mellitus with nephropathy
261008	C108B00	Insulin dependent diabetes mellitus with mononeuropathy
297732	C106100	Diabetes mellitus, adult onset, neurological manifestation
206455	C108000	Insulin-dependent diabetes mellitus with renal complications
309524	C109H00	Non-insulin dependent d m with neuropathic arthropathy
251806	C108200	Insulin-dependent diabetes mellitus with neurological comps
343081	C10F100	Type 2 diabetes mellitus with ophthalmic complications
341814	2BBQ.00	O/E - left eye background diabetic retinopathy
309275	C109011	Type II diabetes mellitus with renal complications
252191	F420200	Preproliferative diabetic retinopathy
288456	C105000	Diabetes mellitus, juvenile type, ophthalmic manifestation
347472	C10FR00	Type 2 diabetes mellitus with gastroparesis
288461	C109100	Non-insulin-dependent diabetes mellitus with ophthalm comps
306132	250 F	Neuropathy Diabetic
341286	C10FE00	Type 2 diabetes mellitus with diabetic cataract
308948	C108712	Type 1 diabetes mellitus with retinopathy
242643	C106.13	Diabetes mellitus with polyneuropathy
279760	F420.00	Diabetic retinopathy

Medcodes	Read code	Description
308463	C109612	Type 2 diabetes mellitus with retinopathy
270274	C109B00	Non-insulin dependent diabetes mellitus with polyneuropathy
309943	F420600	Non proliferative diabetic retinopathy
288457	C105y00	Other specified diabetes mellitus with ophthalmic complicatn
309614	C109E11	Type II diabetes mellitus with diabetic cataract
341801	C10FB00	Type 2 diabetes mellitus with polyneuropathy
340973	C10FA00	Type 2 diabetes mellitus with mononeuropathy
347417	C10F611	Type II diabetes mellitus with retinopathy
343003	C10E200	Type 1 diabetes mellitus with neurological complications
342681	C108B11	Type I diabetes mellitus with mononeuropathy
206459	C109600	Non-insulin-dependent diabetes mellitus with retinopathy
298103	F381300	Myasthenic syndrome due to diabetic amyotrophy
224505	C106z00	Diabetes mellitus NOS with neurological manifestation
224503	C104y00	Other specified diabetes mellitus with renal complications
342469	2BBV.00	O/E - left eye proliferative diabetic retinopathy
332953	C108711	Type I diabetes mellitus with retinopathy
279761	F420400	Diabetic maculopathy
201928	250 LG	Diabetic Glomerulosclerosis
309628	C109C12	Type 2 diabetes mellitus with nephropathy
224504	C106.11	Diabetic amyotrophy
207385	K01x111	Kimmelstiel - Wilson disease
206456	C108D00	Insulin dependent diabetes mellitus with nephropathy
341836	C108212	Type 1 diabetes mellitus with neurological complications
242645	C108100	Insulin-dependent diabetes mellitus with ophthalmic comps
288858	F3y0.00	Diabetic mononeuropathy
252174	F372.12	Diabetic neuropathy
234015	F420300	Advanced diabetic maculopathy
347410	C10F011	Type II diabetes mellitus with renal complications
344952	2BBI.00	O/E - left eye stable treated prolif diabetic retinopathy
339960	C10FC00	Type 2 diabetes mellitus with nephropathy
343345	C10EF00	Type 1 diabetes mellitus with diabetic cataract
308504	C109E12	Type 2 diabetes mellitus with diabetic cataract
309757	C108D11	Type I diabetes mellitus with nephropathy
308851	C109B11	Type II diabetes mellitus with polyneuropathy

Medcodes	Read code	Description
341264	C10F200	Type 2 diabetes mellitus with neurological complications
346403	C10EB00	Type 1 diabetes mellitus with mononeuropathy
309007	C109H12	Type 2 diabetes mellitus with neuropathic arthropathy
333002	F420800	High risk non proliferative diabetic retinopathy
242647	C108700	Insulin dependent diabetes mellitus with retinopathy
341800	C10EC00	Type 1 diabetes mellitus with polyneuropathy
219965	250 M	Charcot's Diabetic Arthropathy
261411	F374z00	Polyneuropathy in disease NOS
309758	C109112	Type 2 diabetes mellitus with ophthalmic complications
306133	250 N	Diabetic Nephropathy
309796	2BBL.00	O/E - diabetic maculopathy present both eyes
331538	C109012	Type 2 diabetes mellitus with renal complications
242648	C109000	Non-insulin-dependent diabetes mellitus with renal comps
206458	C109200	Non-insulin-dependent diabetes mellitus with neuro comps
341701	F420700	High risk proliferative diabetic retinopathy
215440	C106.12	Diabetes mellitus with neuropathy
342045	2BBS.00	O/E - left eye preproliferative diabetic retinopathy
340163	C109E00	Non-insulin depend diabetes mellitus with diabetic cataract
340357	C10F600	Type 2 diabetes mellitus with retinopathy
297737	C108C00	Insulin dependent diabetes mellitus with polyneuropathy
336008	C108211	Type I diabetes mellitus with neurological complications
340987	C10E000	Type 1 diabetes mellitus with renal complications
310061	C109H11	Type II diabetes mellitus with neuropathic arthropathy
297731	C106.00	Diabetes mellitus with neurological manifestation
308830	C109611	Type II diabetes mellitus with retinopathy
233989	F372.11	Diabetic polyneuropathy
344951	2BBk.00	O/E - right eye stable treated prolif diabetic retinopathy
243072	F420z00	Diabetic retinopathy NOS
288458	C105z00	Diabetes mellitus NOS with ophthalmic manifestation
233604	C105100	Diabetes mellitus, adult onset, ophthalmic manifestation
340333	C10ED00	Type 1 diabetes mellitus with nephropathy
308871	C108F11	Type I diabetes mellitus with diabetic cataract
331568	C108011	Type I diabetes mellitus with renal complications
346291	C10FC11	Type II diabetes mellitus with nephropathy

Medcodes	Read code	Description
340162	C108012	Type 1 diabetes mellitus with renal complications
340507	C109A11	Type II diabetes mellitus with mononeuropathy
252180	F381311	Diabetic amyotrophy
308872	C109C11	Type II diabetes mellitus with nephropathy
347405	C10EQ00	Type 1 diabetes mellitus with gastroparesis
279345	C109A00	Non-insulin dependent diabetes mellitus with mononeuropathy
308715	C108F00	Insulin dependent diabetes mellitus with diabetic cataract
206453	C104.11	Diabetic nephropathy
342033	2BBR.00	O/E - right eye preproliferative diabetic retinopathy
333621	C108J12	Type 1 diabetes mellitus with neuropathic arthropathy
347771	C10FB11	Type II diabetes mellitus with polyneuropathy
297733	C106y00	Other specified diabetes mellitus with neurological comps
256383	250 LK	Kimmelstiel- Wilson Disease/Syndrome
340257	C10FH00	Type 2 diabetes mellitus with neuropathic arthropathy
341459	C10F000	Type 2 diabetes mellitus with renal complications
297730	C105.00	Diabetes mellitus with ophthalmic manifestation
261428	F420100	Proliferative diabetic retinopathy
333249	C109211	Type II diabetes mellitus with neurological complications
261003	C104z00	Diabetes mellitis with nephropathy NOS
341221	C10E100	Type 1 diabetes mellitus with ophthalmic complications

10. Read codes to identify dyspnoea

Medcode	Read_code	Description
3092	R060A00	[D]Dyspnoea
6434	1736.00	Paroxysmal nocturnal dyspnoea
7000	2322.00	O/E - dyspnoea
18116	173D.00	Nocturnal dyspnoea
53771	173C.11	Dyspnoea on exertion

11. Read codes to identify ventilator requirement

Medcode	Read_code	Description
87337	7M36300	Ventilatory support

12. Read codes to identify COPD

Medcode	Read code	Description
1001	H3...00	Chronic obstructive pulmonary disease
9520	66YB.00	Chronic obstructive pulmonary disease monitoring
9876	H38..00	Severe chronic obstructive pulmonary disease
10802	H37..00	Moderate chronic obstructive pulmonary disease
10863	H36..00	Mild chronic obstructive pulmonary disease
11287	66YM.00	Chronic obstructive pulmonary disease annual review
18621	66YL.00	Chronic obstructive pulmonary disease follow-up
37247	H3z..11	Chronic obstructive pulmonary disease NOS
45770	66Yg.00	Chronic obstructive pulmonary disease disturbs sleep
45771	66Yh.00	Chronic obstructive pulmonary disease does not disturb sleep
65733	Hyu3100	[X]Other specified chronic obstructive pulmonary disease
67040	H3y..11	Other specified chronic obstructive pulmonary disease
93568	H39..00	Very severe chronic obstructive pulmonary disease
102685	66YB000	Chronic obstructive pulmonary disease 3 monthly review
103007	66YB100	Chronic obstructive pulmonary disease 6 monthly review
103494	14B3.12	History of chronic obstructive pulmonary disease
104985	9NgP.00	On chronic obstructive pulmonary disease supprtv cre pathway
105457	8CMW500	Chronic obstructive pulmonary disease care pathway

13. Read codes to identify heart failure

Medcode	Read_code	Description
398	G580.00	Congestive heart failure
2062	G58..00	Heart failure
4024	G58z.00	Heart failure NOS
9913	1O1..00	Heart failure confirmed
10079	G580.12	Right heart failure
15058	14A6.00	H/O: heart failure
17851	8HBE.00	Heart failure follow-up
21837	G232.00	Hypertensive heart&renal dis wth (congestive) heart failure
23707	G580000	Acute congestive heart failure
27964	G582.00	Acute heart failure
28684	G233.00	Hypertensive heart and renal disease with renal failure
30779	662W.00	Heart failure annual review
32671	G580100	Chronic congestive heart failure

Medcode	Read_code	Description
32898	8H2S.00	Admit heart failure emergency
32911	9Or..00	Heart failure monitoring administration
32945	8CL3.00	Heart failure care plan discussed with patient
46912	14AM.00	H/O: Heart failure in last year
60099	67D4.00	Heart failure information given to patient
66306	SP11111	Heart failure as a complication of care
69062	9N6T.00	Referred by heart failure nurse specialist
71235	8Hk0.00	Referred to heart failure education group
83502	662p.00	Heart failure 6 month review
94870	G580400	Congestive heart failure due to valvular disease
96799	G5y4z00	Post cardiac operation heart failure NOS
101137	G583.11	HFNEF - heart failure with normal ejection fraction
101138	G583.00	Heart failure with normal ejection fraction
103732	8CMK.00	Has heart failure management plan
105002	679W100	Education about deteriorating heart failure
105542	8CeC.00	Preferred place of care for next exacerbation heart failure
106198	661M500	Heart failure self-management plan agreed

14. Read codes to identify renal failure

Medcode	Read_code	Description
350	K06..00	Renal failure unspecified
512	K05..00	Chronic renal failure
2266	K04..00	Acute renal failure
6712	K050.00	End stage renal failure
11554	SP15400	Renal failure as a complication of care
11773	7L1A.11	Dialysis for renal failure
15945	SK05.00	Renal failure following crush syndrome
16929	D215.00	Anaemia secondary to renal failure
24292	SP15412	Post operative renal failure
24676	SK08.00	Acute renal failure due to rhabdomyolysis
25394	D215000	Anaemia secondary to chronic renal failure
25582	K04z.00	Acute renal failure NOS
28684	G233.00	Hypertensive heart and renal disease with renal failure
31549	7L1A.00	Compensation for renal failure
32423	G222.00	Hypertensive renal disease with renal failure

Medcode	Read_code	Description
35235	K04y.00	Other acute renal failure
48022	7L1Ay00	Other specified compensation for renal failure
53852	K05..12	End stage renal failure
53940	Kyu2100	[X]Other chronic renal failure
53945	Kyu2000	[X]Other acute renal failure
56760	7L1B.00	Placement ambulatory apparatus compensation renal failure
57919	K043.00	Acute drug-induced renal failure
59194	7L1By00	Placement ambulatory apparatus- compensate renal failure OS
61930	Kyu2.00	[X]Renal failure
63277	L393.00	Acute renal failure following labour and delivery
63760	SK05.11	Renal failure after crushing
64636	7L1Az00	Compensation for renal failure NOS
65089	7L1Cz00	Placement other apparatus- compensate for renal failure NOS
71314	L093.00	Renal failure following abortive pregnancy
72458	L393000	Post-delivery acute renal failure unspecified
83513	7L1C.00	Placement other apparatus for compensation for renal failure
96179	L393100	Post-delivery acute renal failure - delivered with p/n prob
97198	K044.00	Acute renal failure due to urinary obstruction
100205	K0E..00	Acute-on-chronic renal failure
101666	L070300	Unspecified abortion with renal failure
104857	K043000	Acute renal failure due to ACE inhibitor
105209	K045.00	Acute renal failure due to non-traumatic rhabdomyolysis
105267	K04B.00	Acute renal failure due to traumatic rhabdomyolysis
105739	K04..11	ARF - Acute renal failure
106860	C353600	Renal failure-associated hyperphosphataemia
107241	K043400	Acute renal failure induced by non-steroid anti-inflamm drug

15. Read codes to identify hypertension

Medcode	Read_code	Description
799	G20..00	Essential hypertension
1894	G201.00	Benign essential hypertension
2666	14A2.00	H/O: hypertension
3425	662O.00	On treatment for hypertension
3712	G20z.11	Hypertension NOS
4372	G202.00	Systolic hypertension

Medcode	Read_code	Description
7329	G24..00	Secondary hypertension
10818	G20z.00	Essential hypertension NOS
12680	8CR4.00	Hypertension clinical management plan
15377	G200.00	Malignant essential hypertension
16059	G24z.00	Secondary hypertension NOS
16565	6627	Good hypertension control
18482	662c.00	Hypertension six month review
18590	662b.00	Moderate hypertension control
19070	662d.00	Hypertension annual review
21826	662F.00	Hypertension treatm. started
25371	G241000	Secondary benign renovascular hypertension
27511	6628	Poor hypertension control
30776	6629	Hypertension:follow-up default
31387	G24z000	Secondary renovascular hypertension NOS
31755	G240.00	Secondary malignant hypertension
34744	G244.00	Hypertension secondary to endocrine disorders
42229	G24zz00	Secondary hypertension NOS
44549	L128.00	Pre-exist hypertension compl preg childbirth and puerperium
51635	G241z00	Secondary benign hypertension NOS
57288	G241.00	Secondary benign hypertension
59383	G240000	Secondary malignant renovascular hypertension
73293	G240z00	Secondary malignant hypertension NOS
83473	G203.00	Diastolic hypertension
85944	7Q01.00	High cost hypertension drugs
97533	Gyu2100	[X]Hypertension secondary to other renal disorders
98230	67H8.00	Lifestyle advice regarding hypertension
101649	7Q01y00	Other specified high cost hypertension drugs
102406	662P000	Hypertension 9 month review
102458	Gyu2000	[X]Other secondary hypertension
105274	G28..00	Stage 2 hypertension (NICE - Nat Ins for Hth Clin Excl 2011)
105316	G25..11	Stage 1 hypertension
105371	G25..00	Stage 1 hypertension (NICE - Nat Ins for Hth Clin Excl 2011)
105480	G27..00	Hypertension resistant to drug therapy
105487	G26..11	Severe hypertension

Medcode	Read_code	Description
105989	G26..00	Severe hypertension (Nat Inst for Health Clinical Ex 2011)
61166	G21z000	Hypertensive heart disease NOS without CCF
61660	G211000	Benign hypertensive heart disease without CCF
95334	G210000	Malignant hypertensive heart disease without CCF

16. Codes to identify open and closed tibial shaft fracture

Medcode	Read_code	Description
20678	S333200	Open fracture of tibia and fibula, shaft
28068	S333.00	Open fracture of tibia/fibula, shaft
28118	S333000	Open fracture shaft of tibia
28198	S333z00	Open fracture of tibia and fibula, shaft, NOS
28233	S33y.00	Open fracture of tibia and fibula, unspecified part, NOS
29084	S33y200	Open fracture of tibia and fibula, unspecified part
29164	S33y000	Open fracture of tibia, unspecified part, NOS

Medcode	Read_code	Description
971	S33x000	Closed fracture of tibia, unspecified part, NOS
4572	S33x200	Closed fracture of tibia and fibula, unspecified part
29109	S33x.00	Closed fracture of tibia and fibula, unspecified part, NOS
29121	S332.00	Closed fracture of tibia/fibula, shaft
33520	S332200	Closed fracture of tibia and fibula, shaft
34021	S332000	Closed fracture shaft of tibia
41971	S33xz00	Closed fracture of tibia and fibula, unspecified part, NOS
55464	S332z00	Closed fracture of tibia and fibula, shaft, NOS

OPCS-4	Description	Open/closed fracture
S571	Debridement of skin NEC	Open
W332	Debridement of open fracture of bone	Open
T963	Debridement of soft tissue NEC	Open
W336	Debridement of bone NEC	Open

ICD-10	Description	Open/closed fracture
T14.1	Open wound of unspecified body region	Open
T01.3	Open wounds involving multiple regions of lower limb(s)	Open
S81.7	Multiple open wounds of lower leg	Open

ICD-10	Description	Open/closed fracture
S81.8	Open wound of other parts of lower leg	Open
S81.9	Open wound of lower leg, part unspecified	Open
T93.0	Sequelae of open wound of lower limb	Open
T93.2	Sequelae of other fractures of lower limb	Open
T01.9	Multiple open wounds, unspecified	Open
T13.1	Open wound of lower limb, level unspecified	Open
T01.8	Open wounds involving other combinations of body regions	Open
T94.0	Sequelae of injuries involving multiple body regions	Open
T94.1	Sequelae of injuries, not specified by body region	Open
T12.1	Fracture of lower limb, level unspecified, open	Open

17. Read codes to identify Charlson comorbidity index

Microsoft Excel 2003 Worksheet

18. OPCS Codes to identify reoperations

OPCS-4	Description
W242	Closed reduction of fracture of long bone and rigid internal fixation NEC
O172	Remanipulation of fracture of long bone and rigid internal fixation NEC
O173	Remanipulation of fracture of long bone and flexible internal fixation HFQ
O175	Remanipulation of fragment of bone and fixation using screw
O178	Other specified secondary closed reduction of fracture of bone and internal fixation
O179	Unspecified secondary closed reduction of fracture of bone and internal fixation
W231	Secondary open reduction of fracture of bone and intramedullary fixation HFQ
W232	Secondary open reduction of fracture of bone and extramedullary fixation HFQ
W236	Secondary open reduction of fracture of bone and internal fixation HFQ
W248	Other specified closed reduction of fracture of bone and internal fixation
W249	Unspecified closed reduction of fracture of bone and internal fixation
W281	Application of internal fixation to bone NEC
W282	Adjustment to internal fixation of bone NEC
W283	Removal of internal fixation from bone NEC
W288	Other specified other internal fixation of bone
W289	Unspecified other internal fixation of bone

OPCS-4	Description
W235	Secondary open reduction of fracture of bone and external fixation HFQ
W252	Closed reduction of fracture of bone and fixation using functional bracing system
W253	Remanipulation of fracture of bone and external fixation HFQ
W258	Other specified closed reduction of fracture of bone and external fixation
W259	Unspecified closed reduction of fracture of bone and external fixation
W301	Application of external fixation to bone NEC
W302	Adjustment to external fixation of bone NEC
W303	Removal of external fixation from bone NEC
W304	Application of external ring fixation to bone NEC
W308	Other specified other external fixation of bone
W309	Unspecified other external fixation of bone
W35.3	Removal of implanted substance from bone
W32	Other graft of bone
W32.1	Prepared graft of bone
W32.2	Allograft of bone NEC
W32.3	Xenograft of bone
W32.4	Synthetic graft of bone
W32.5	Cancellous chip allograft of bone
W32.8	Other specified other graft of bone
W32.9	Unspecified other graft of bone
S31.3	Revision of flap of skin NEC

Additional file 2: Baseline and results at all time points

Table C1. Patient demographic and clinical characteristics at all time points

	All enrolled patients (N=805)	Index stay			30 days			90 days			1 year			2 years		
		No infection (N=775)	Infection (N=30)	p-value[a]	No infection (N=736)	Infection (N=64)	p-value[a]	No infection (N=699)	Infection (N=71)	p-value[a]	No infection (N=606)	Infection (N=80)	p-value[a]	No infection (N=509)	Infection (N=79)	p-value[a]
Demographics																
Age (years), mean (SD)	40.8 (17.2)	40.7 (16.8)	43.0 (23.9)	0.61	40.5 (16.9)	44.0 (19.1)	0.17	40.7 (16.9)	43.8 (19.1)	0.20	40.7 (16.8)	45.1 (19.1)	0.06	40.5 (16.4)	46.4 (20.0)	0.02
Gender, n (%)				0.84			1.00			1.00			0.89			1.00
Male	590 (73.3)	569 (73.4)	21 (70.0)		539 (73.2)	47 (73.4)		508 (72.7)	52 (73.2)		438 (72.3)	59 (73.8)		368 (72.3)	57 (72.2)	
Clinical history/comorbidities																
Charlson score, mean (SD)	0.04 (0.23)	0.04 (0.24)	0.00 (0.00)	<0.001	0.04 (0.24)	0.02 (0.12)	0.22	0.04 (0.3)	0.01 (0.12)	0.13	0.04 (0.24)	0.01 (0.11)	0.11	0.03 (0.22)	0.01 (0.11)	0.25
Smoker, n (%)	256 (31.8)	247 (31.9)	9 (30.0)	0.99	239 (32.5)	17 (26.6)	0.41	233 (33.3)	18 (25.4)	0.22	202 (33.3)	20 (25.0)	0.17	160 (31.4)	19 (24.1)	0.23
Diabetes, n (%)	27 (3.4)	27 (3.5)	0 (0.0)	0.62	26 (3.5)	1 (1.6)	0.72	26 (3.7)	1 (1.4)	0.50	21 (3.5)	3 (3.8)	0.75	15 (3.0)	3 (3.8)	0.72
COPD, n (%)	8 (1.0)	8 (1.0)	0 (0.0)	1.00	8 (1.1)	0 (0.0)	1.00	7 (1.0)	0 (0.0)	1.00	6 (1.0)	1 (1.3)	0.58	3 (0.6)	1 (1.3)	0.44
Congestive heart failure, n (%)	2 (0.3)	2 (0.3)	0 (0.0)	1.00	2 (0.3)	0 (0.0)	1.00	1 (0.1)	0 (0.0)	1.00	0 (0.0)	0 (0.0)	NA	0 (0.0)	0 (0.0)	NA
Hypertension, n (%)	12 (1.5)	12 (1.6)	0 (0.0)	1.00	12 (1.6)	0 (0.0)	0.61	12 (1.7)	0 (0.0)	0.62	10 (1.7)	0 (0.0)	0.62	7 (1.4)	0 (0.0)	0.60
Compartment syndrome, n (%)	27 (3.4)	22 (2.8)	5 (16.7)	0.00	19 (2.6)	8 (12.5)	<0.05	18 (2.6)	8 (11.3)	<0.05	17 (2.8)	9 (11.2)	0.00	15 (3.0)	8 (10.1)	<0.05
Index episode																
Year of intramedullary nailing, mean (SD)	2009 (3.6)	2009 (3.6)	2009 (3.6)	0.72	2009 (3.6)	2009 (3.6)	0.99	2009 (3.6)	2009 (3.6)	0.74	2008 (3.4)	2008 (3.4)	0.99	2008 (3.1)	2008 (3.1)	0.85
Inpatient waiting time (days) for surgery, mean (SD)	1.4 (2.4)	1.4 (2.4)	0.7 (2.4)	0.14	1.4 (2.4)	0.7 (1.7)	<0.05	1.4 (2.5)	0.8 (1.7)	<0.05	1.4 (2.4)	0.6 (1.0)	<0.001	1.4 (2.2)	0.6 (1.0)	<0.001
Fracture type, n (%)				<0.001			<0.001			<0.001			<0.001			<0.001
Closed fracture	663 (82.4)	648 (83.6)	15 (50.0)		624 (84.8)	35 (54.7)		595 (85.1)	42 (59.2)		524 (86.5)	49 (61.3)		438 (86.1)	52 (65.8)	

	All enrolled patients (N=805)	Index stay			30 days			90 days			1 year			2 years		
		No infection (N=775)	Infection (N=30)	p-value[a]	No infection (N=736)	Infection (N=64)	p-value[a]	No infection (N=699)	Infection (N=71)	p-value[a]	No infection (N=606)	Infection (N=80)	p-value[a]	No infection (N=509)	Infection (N=79)	p-value[a]
Received ≥1 prescription for antibiotics in the 12 months prior to the index stay, n (%)	60 (7.5)	60 (7.7)	0 (0.0)	0.16	57 (7.7)	3 (4.7)	0.47	56 (8.0)	3 (4.2)	0.36	47 (7.8)	4 (5.0)	0.51	35 (6.9)	5 (6.3)	1.000
Received ≥1 prescription for opioids in the 12 months prior to the index stay, n (%)	16 (2.0)	15 (1.9)	1 (3.3)	0.46	15 (2.0)	1 (1.6)	1.00	15 (2.2)	1 (1.4)	1.00	11 (1.8)	2 (2.5)	0.66	8 (1.6)	2 (2.5)	0.63

Abbreviations: COPD, chronic obstructive pulmonary disease; NA, not applicable; SD, standard deviation.

[a] No infection versus infection, t-tests were performed for comparison of continuous variables and chi-squared (or Fisher exact tests when n was <5) for comparison of categorical variables.

Table D1. Comparative results at all time points

Time period	Endpoint	Bivariate analysis, mean (SD)		Multivariate analysis, mean (95% CI)		Absolute difference (multivariate analysis)
		Infection	No infection	Infection	No infection	
Index stay *(N infection = 30; N no infection = 775)*	Total costs (£)	11,695 (6,553)	6,669 (3,133; p<0.001)	10,384 (8,900, 12,116)	6,603 (6,411, 6,802)	3,781 p<0.001
	Inpatient costs (£)	11,695 (6,553)	6,669 (3,133; p<0.001)	10,384 (8,900, 12,116)	6,603 (6,411, 6,802)	3,781 p<0.001
	LOS (days)	22.6 (20.0)	9.7 (12.1; p<0.001)	17.6 (13.0, 23.7)	8.5 (8.0, 9.0)	9.05 p<0.001
	ICU LOS (days)	1.5 (8.2)	0.1 (1.1; p=0.53)	0.1 (0.1, 0.2)	0.0 (0.0, 0.01)	0.115 p<0.001
	Reoperations (number)	0.3 (0.8)	0.0 (0.1; p<0.001)	0.1 (0.0, 0.2)	0.0 (0.0, 0.0)	0.070 p<0.001
	Reoperations (rate, %)	13.3	1.3 (p<0.001)	9.7 (3.1, 26.3)	1.1 (0.5, 2.1)	8.6 p<0.001

Time period	Endpoint	Bivariate analysis, mean (SD)		Multivariate analysis, mean (95% CI)		Absolute difference (multivariate analysis)
		Infection	No infection	Infection	No infection	
Index stay + 30 days post-discharge *(N infection = 64; N no infection = 736)*	Total costs (£)	12,673 (7,345)	7,089 (3,588; p<0.001)	11,257 (10,045, 12,615)	7,017 (6,792, 7,248)	4,241 p<0.001
	Inpatient costs (£)	12,367 (7,290)	6,829 (3,397; p<0.001)	11,008 (9,818, 12,343)	6,768 (6,551, 6,993)	4,240 p<0.001
	Hospital outpatient/ambulatory costs (£)	215 (116)	155 (94; p=0.4)	245 (145, 345)	152 (125, 179)	93 p=0.07
	Primary care costs (£)	289 (555)	254 (673, p=0.24)	243 (139, 426)	205 (175, 241)	38 p=0.57
	LOS (days)	19.3 (19.2)	10.1 (12.2; p<0.001)	15.0 (12.1, 18.6)	8.9 (8.4, 9.5)	6.1 p<0.001
	ICU LOS (days)	0.7 (5.6)	0.1 (1.1; p=0.4)	0.1 (0.0, 0.1)	0.0 (0.0, 0.0)	0.0 p<0.001
	Readmissions (number)	0.6 (0.6)	0.1 (0.3; p<0.001)	0.5 (0.4, 0.7)	0.1 (0.1, 0.1)	0.4 p<0.001
	Readmissions (rate, %)	48.4	7.6 (p<0.001)	44.1 (31.5, 57.5)	7.1 (5.4, 9.2)	37.0 p<0.001
	Reoperations (number)	0.2 (0.7)	0.0 (0.1; p<0.001)	0.1 (0.1, 0.2)	0.0 (0.0, 0.0)	0.1 p<0.001
	Reoperations (rate, %)	14.1	1.6 (p<0.001)	11.5 (5.4, 22.9)	1.3 (0.7, 2.5)	10.2 p<0.001
	Amputation (rate, %)	3.1	0.1 (p<0.01)	Not feasible		
	Hospital outpatient/ambulatory referrals (number)	1.6 (0.9)	1.2 (0.5; p=0.28)	1.6 (1.1, 2.2)	1.21 (1.0, 1.4)	0.45 p=0.13
Index stay + 90 days post-discharge *(N infection = 71; N no*	Total costs (£)	13,621 (7,827)	7,527 (4,326; p<0.001)	11,949 (10,634,13,427)	7,423 (7,160, 7,696)	4,526 p<0.001
	Inpatient costs (£)	13,154 (7,673)	7,157 (4,111; p<0.001)	11,532 (10,246,12,979)	7,072 (6,818, 7,336)	4,459 p<0.001

Time period	Endpoint	Bivariate analysis, mean (SD)		Multivariate analysis, mean (95% CI)		Absolute difference (multivariate analysis)
		Infection	No infection	Infection	No infection	
infection = 699)	Hospital outpatient/ambulatory costs (£)	183 (87)	171 (135; p=0.53)	194 (125, 264)	170 (141, 198)	25 p=0.515
	Primary care costs (£)	436 (637)	353 (737; p<0.05)	428 (290, 630)	299 (264, 338)	129 p=0.084
	LOS (days)	21.7 (21.5)	11.1 (14.6 p<0.001)	16.4 (13.2, 20.4)	9.6 (9.0, 10.3)	6.8 p<0.001
	ICU LOS (days)	0.7 (5.3)	0.1 (1.2; p=0.576)	0.0 (0.0, 0.1)	0.0 (0.0, 0.0)	0.0 p<0.001
	Readmissions (number)	0.8 (0.8)	0.2 (0.6; p<0.001)	0.7 (0.5, 0.9)	0.2 (0.2, 0.2)	0.5 p<0.001
	Readmissions (rate, %)	57.7	17.2 (p<0.001)	5.4 (41.5, 65.9)	16.5 (13.9, 19.5)	37.4 p<0.001
	Reoperations (number)	0.3 (0.7)	0.1 (0.3; p<0.001)	0.2 (0.1, 0.3)	0.1 (0.0, 0.1)	0.1 p=0.001
	Reoperations (rate, %)	18.3	6.0 (p<0.001)	14.3 (7.7, 25.0)	5.4 (3.9, 7.4)	9.0 p<0.05
	Amputation (rate, %)	2.8	0.1 (p<0.05)	Not feasible		
	Hospital outpatient/ambulatory referrals (number)	1.2 (0.6)	1.4 (0.9; p=0.92)	1.3 (0.9, 1.7)	1.4 (1.2, 1.5)	0.0 p=0.835
Index stay + 1 year post-discharge *(N infection = 80; N no infection = 606)*	Total costs (£)	16,800 (12,663)	8,435 (5,330; p<0.001)	14,756 (13,123, 16,593)	8,279 (7,946, 8,626)	6,478 p<0.001
	Inpatient costs (£)	15,580 (11,872)	7,746 (5,060; p<0.001)	13,672 (12,122, 15,420)	7,616 (7,301, 7,944)	6,056 p<0.001
	Hospital outpatient/ambulatory costs (£)	250 (251)	239 (218; p=0.77)	220 (151, 288)	244 (211, 277)	25 p=0.516
	Primary care costs (£)	1,139 (1,657)	630 (903; p<0.001)	1,017 (769, 1,344)	551 (498, 609)	466 p<0.001

Time period	Endpoint	Bivariate analysis, mean (SD)		Multivariate analysis, mean (95% CI)		Absolute difference (multivariate analysis)
		Infection	No infection	Infection	No infection	
	LOS (days)	28.5 (33.3)	12.6 (21.3; p<0.001)	21.9 (17.3, 27.7)	10.5 (9.7, 11.4)	11.4 p<0.001
	ICU LOS (days)	0.2 (1.5)	0.1 (1.1; p=0.758)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 p=0.914
	Readmissions (number)	1.5 (1.5)	0.5 (0.9; p<0.001)	1.5 (1.2, 1.8)	0.5 (0.4, 0.6)	1.0 p<0.001
	Readmissions (rate, %)	75	36 (p<0.001)	74.4 (63.4, 83.0)	35.9 (32.1, 39.9)	38.5 p<0.001
	Reoperations (number)	0.6 (1.0)	0.2 (0.5; p<0.001)	0.6 (0.5, 0.8)	0.2 (0.2, 0.3)	0.4 p<0.001
	Reoperations (rate, %)	37.5	21.3 (p<0.01)	38.6 (28.3, 50.0)	20.3 (17.2, 23.8)	18.2 p<0.001
	Amputation (rate, %)	2.5	0.2 (p<0.05)	Not feasible		
	Hospital outpatient/ambulatory referrals (number)	1.8 (1.6)	1.8 (1.5; p=0.66)	1.7 (1.2, 2.1)	1.8 (1.6, 2.1)	0.2 p=0.44
Index stay + 2 years post-discharge *(N infection = 79; N no infection = 509)*	Total costs (£)	18,779 (14,929)	9,611 (6,284; p<0.001)	16,626 (14,664, 18,849)	9,439 (8,998, 9,901)	7,187 p<0.001
	Inpatient costs (£)	16,900 (13,720)	8,573 (5,729; p<0.001)	14,898 (13,106, 16,935)	8,447 (8,044, 8,871)	6,451 p<0.001
	Hospital outpatient/ambulatory costs (£)	282 (296)	275 (265; p=0.893)	264 (189, 338)	277 (243, 310)	13 p=0.747
	Primary care costs (£)	1,758 (2,437)	929 (1,179; p<0.01)	1,487 (1,149, 1,924)	821 (742, 907)	666 p<0.001
	LOS (days)	31.5 (38.1)	13.4 (22.6; p<0.001)	24.6 (19.6, 30.8)	11.3 (10.4, 12.3)	13.3 p<0.001
	ICU LOS (days)	0.2 (1.5)	0.1 (1.2; p=0.24)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 p=0.20

Time period	Endpoint	Bivariate analysis, mean (SD)		Multivariate analysis, mean (95% CI)		Absolute difference (multivariate analysis)
		Infection	No infection	Infection	No infection	
	Readmissions (number)	2.1 (2.3)	1.0 (1.5; p<0.001)	2.2 (1.9, 2.6)	0.9 (0.8, 1.0)	1.3 p<0.001
	Readmissions (rate, %)	77.2	51.1 (p<0.001)	77.6 (67.0, 85.6)	51.4 (46.9, 56.8)	26.3 p<0.001
	Reoperations (number)	0.8 (1.1)	0.4 (0.7; p<0.01)	0.8 (0.6, 1.0)	0.4 (0.3, 0.4)	0.4 p<0.001
	Reoperations (rate, %)	46.8	32.4 (p<0.05)	49.0 (37.7, 60.3)	31.2 (27.2, 35.5)	17.7 p<0.05
	Amputation (rate, %)	3.8	0.2 (p<0.01)	Not feasible		
	Hospital outpatient/ambulatory referrals (number)	2.0 (2.0)	2.1 (1.9; p=0.55)	2.0 (1.5, 2.5)	2.1 (1.8, 2.3)	0.1 p=0.82

Abbreviations: CI, confidence interval; ICU, intensive care unit; LOS, length of stay; NA, not applicable; SD, standard deviation.

Table D2. 1 year cost breakdown (£) – inpatient setting

Endpoint	Bivariate analysis, mean (SD)	
	Infection	No infection
Total inpatient costs	15,580 (11,872)	7,746 (5,060)
HRG costs	15,488 (11,743)	7,702 (4,985)
Unbundled HRG costs	36 (116)	16 (72)
Critical care costs	56 (381)	26 (208)
Specialised care costs	0 (0)	2 (42)

Abbreviations: HRG, Healthcare Resource Group; SD, standard deviation.

Table D3. 1 year healthcare resource use and cost breakdown – primary care

Endpoint	Bivariate analysis, mean (SD)	
	Infection	No infection
Costs (£)		
Total primary care costs	1,139 (1,657)	630 (903)
Total drug costs	368 (1,031)	198 (681)
Total test costs	147 (247)	95 (186)
Imaging test costs	27 (71)	25 (72)
Total consultation costs	625 (721)	338 (334)
GP	322 (317)	212 (225)
Nurse	140 (362)	36 (75)
Other healthcare professional	120 (243)	55 (121)
Administrative	42 (36)	35 (30)
Healthcare resource use (number)		
Total tests	25 (52)	14 (30)
Imaging tests	0.4 (0.8)	0.5 (1.5)
Total consultations	52 (51)	33 (25)
GP	14 (13)	9 (9)
Nurse	10 (21)	3 (5)
Other healthcare professional	9 (17)	4 (8)
Administrative	22 (18)	18 (15)

Abbreviations: GP, General Practitioner; SD, standard deviation.

Table D4. Subgroup analyses of 1 year inpatient costs – infection type (deep versus superficial)

	No infection (N=606)	Superficial infection (N=54)	Deep infection (N=26)
Bivariate analysis, mean (SD)	£7,746 (£5,060)	£14,232 (£8,633)	£18,378 (£16,592)
Multivariate analysis, mean (95% CI)[a]	£7,614 (£7,301, £7,941)	£12,814 (£11,093, £14,803)	£15,513 (£12,640, £19,040)

Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; SD, standard deviation.

[a] Adjusted for open/closed fracture, age, smoker, year at index, diabetes, COPD, days prior nailing and compartment syndrome.

Table D5. Subgroup analyses of 1 year inpatient costs – fracture type (open versus closed)

	No infection (N=606)		Infection (N=80)	
Fracture type	**Closed (N=524)**	**Open (N=82)**	**Closed (N=49)**	**Open (N=31)**
Bivariate analysis, mean (SD)	£7,433 (£3,957)	£9,741 (£9,247)	£12,291 (£7,366)	£20,778 (£15,451)
Multivariate analysis, mean (95% CI)[a]	£7,278 (£6,956, £7,614)	£9,495 (£8,469, £10,645)	£12,178 (£10,492, £14,136)	£19,542 (£16,166, £23,623)

Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; SD, standard deviation.

[a] Adjusted for age, smoker, year at index, diabetes, COPD, days prior nailing and compartment syndrome.

Table D6. Sensitivity analyses

Time period	Endpoint	Bivariate analysis, mean (SD)		Multivariate analysis, mean (95% CI)		Absolute difference (multivariate analysis)
		Infection	No infection	Infection	No infection	
Index stay *(N infection = 24; N no infection = 564)*	Total costs (£)	12,554 (6,832)	6,580 (3,123; p<0.001)	11,110 (9,328, 13,232)	6,517 (6,295, 6,747)	4,593 p<0.001
	LOS (days)	24.2 (20.9)	9.4 (11.7; p<0.001)	18.6 (13.1, 26.4)	8.5 (7.9, 9.1)	10.1 p<0.001
	Reoperations (number)	0.3 (0.9)	0.0 (0.1; p<0.001)	0.1 (0.0, 0.3)	0.0 (0.0, 0.0)	0.1 p<0.001
	Reoperations (rate)	12.5	1.6 (p<0.01)	9.9 (2.7, 30.6)	1.4 (0.7, 2.8)	8.5 p<0.05
Index stay + 30 days post-discharge *(N infection = 51; N no infection = 537)*	Total costs (£)	12,957 (7,385)	7,077 (3,747; p<0.001)	11,453 (10,016, 13,096)	7,010 (6,739, 7,292)	4,444 p<0.001
	LOS (days)	20.2 (19.4)	10.0 (12.4; p<0.001)	15.6 (12.1, 20.0)	9.1 (8.4, 9.8)	6.5 p<0.001
	Readmissions (number)	0.6 (0.6)	0.1 (0.3; p<0.001)	0.5 (0.3, 0.7)	0.1 (0.1, 0.1)	0.4 p<0.001
	Readmissions (rate)	47.1	8.4 (p<0.001)	45.7 (32.0, 60.0)	7.9 (5.9, 10.5)	37.8 p<0.001
	Reoperations (number)	0.3 (0.7)	0.0 (0.2; p<0.001)	0.1 (0.1, 0.3)	0.0 (0.0, 0.0)	0.1 p<0.001
	Reoperations (rate)	13.7	2.2 (p<0.001)	11.7 (5.0, 25.3)	1.8 (1.0, 3.4)	9.9 p<0.001
Index stay + 90 days post-discharge *(N infection = 59; N no infection = 529)*	Total costs (£)	13,620 (7,762)	7,584 (4,622; p<0.001)	11,869 (10,364, 13,593)	7,480 (7,160, 7,813)	4,389 p<0.001
	LOS (days)	21.9 (21.8)	11.2 (15.2; p<0.001)	16.3 (12.7, 21.0)	9.8 (9.1, 10.7)	6.5 p<0.001
	Readmissions (number)	0.8 (0.8)	0.2 (0.5; p<0.001)	0.7 (0.5, 0.9)	0.2 (0.2, 0.2)	0.5 p<0.001

Time period	Endpoint	Bivariate analysis, mean (SD)		Multivariate analysis, mean (95% CI)		Absolute difference (multivariate analysis)
		Infection	No infection	Infection	No infection	
	Readmissions (rate)	57.6	18.1 (p<0.001)	54.9 (41.1, 68.0)	17.2 (14.1, 20.8)	37.7 p<0.001
	Reoperations (number)	0.3 (0.7)	0.1 (0.3; p<0.05)	0.2 (0.1, 0.3)	0.1 (0.0, 0.1)	0.1 p<0.05
	Reoperations (rate)	15.3	7.0 (p<0.05)	11.1 (5.2, 22.0)	6.1 (4.3, 8.7)	5.0 p=0.1438
Index stay + 1 year post-discharge *(N infection = 72; N no infection = 516)*	Total costs (£)	16,788 (12,914)	8,449 (5,525; p<0.001)	14,597 (12,841, 16,593)	8,294 (7,920, 8,686)	6,303 p<0.001
	LOS (days)	29.2 (34.6)	12.3 (21.1; p<0.001)	22.5 (17.7, 28.5)	10.3 (9.4, 11.2)	12.2 p<0.001
	Readmissions (number)	1.5 (1.6)	0.5 (0.9; p<0.001)	1.5 (1.2, 1.8)	0.5 (0.4, 0.6)	1.0 p<0.001
	Readmissions (rate)	75.0	35.5 (p<0.001)	75.0 (63.6, 83.8)	35.3 (31.2, 39.6)	39.7 p<0.001
	Reoperations (number)	0.6 (0.9)	0.2 (0.5; p<0.01)	0.5 (0.4, 0.7)	0.2 (0.2, 0.3)	0.3 p<0.001
	Reoperations (rate)	36.1	21.7 (p<0.05)	37.4 (26.7, 49.5)	20.7 (17.3, 24.5)	16.8 p<0.05
Index stay + 2 years post-discharge *(N infection = 79; N no infection = 509)*	Total costs (£)	18,779 (14,929)	9,611 (6,284; p<0.001)	16,626 (14,664, 18,849)	9,439 (8,998, 9,901),	7,187 p<0.001
	LOS (days)	31.5 (38.1)	13.4 (22.6; p<0.001)	24.6 (19.6, 30.8)	11.3 (10.4, 12.3)	13.3 p<0.001
	Readmissions (number)	2.1 (2.3)	1.0 (1.5; p<0.001)	2.2 (1.9, 2.5)	0.9 (0.8, 1.0)	1.3 p<0.001
	Readmissions (rate)	77.2	51.1 (p<0.001)	77.6 (67.0, 85.6)	51.4 (46.9, 55.8)	26.3 p<0.001
	Reoperations (number)	0.8 (1.1)	0.4 (0.7; p<0.01)	0.8 (0.6, 1.0)	0.4 (0.3, 0.5)	0.4 p<0.001

Time period	Endpoint	Bivariate analysis, mean (SD)		Multivariate analysis, mean (95% CI)		Absolute difference (multivariate analysis)
		Infection	No infection	Infection	No infection	
	Reoperations (rate)	46.8	32.4 (p<0.05)	49.0 (37.7, 60.3)	31.2 (27.2, 35.5)	17.7 p<0.05

Abbreviations: CI, confidence interval; LOS, length of stay; NA, not applicable; SD, standard deviation.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5-6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*7:9*
Bias	9	Describe any efforts to address potential sources of bias	9-10
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9-10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9-10
		(*b*) Describe any methods used to examine subgroups and interactions	9-10
		(*c*) Explain how missing data were addressed	9
		(*d*) If applicable, explain how loss to follow-up was addressed	10
		(*e*) Describe any sensitivity analyses	9-10
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10:14
		(b) Give reasons for non-participation at each stage	9
		(c) Consider use of a flow diagram	10
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10-11
		(b) Indicate number of participants with missing data for each variable of interest	10:14
		(c) Summarise follow-up time (eg, average and total amount)	10
Outcome data	15*	Report numbers of outcome events or summary measures over time	10:14
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11:14
		(*b*) Report category boundaries when continuous variables were categorized	10:14
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	14-15
Discussion			
Key results	18	Summarise key results with reference to study objectives	15
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	16
Generalisability	21	Discuss the generalisability (external validity) of the study results	15-16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	17

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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A nonconcurrent cohort study to estimate the economic burden of infections following intramedullary nailing for a tibial shaft fracture in England

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Title: A nonconcurrent cohort study to estimate the economic burden of infections following intramedullary nailing for a tibial shaft fracture in England

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Running head:

Resource use and costs in patients with and without infection after tibial fracture nailing

Key words:

- Tibial shaft fracture
- CPRD
- HES
- Infection
- Cost
- England

- Trauma
- Burden of disease

Abstract

Objectives

Determine the impact of infections on direct costs and healthcare resource use in England for patients undergoing intramedullary nailing (IMN) for tibial shaft fractures.

Design

Nonconcurrent cohort based on retrospectively collected data with 2 years follow-up.

Setting

England.

Participants

The study population included adult patients (≥18 years) in England with a diagnosis of tibial shaft fracture (ICD-10, S822) in the inpatient setting between May 2003 and June 2017 followed by a procedure for IMN for tibial shaft fracture within 30 days. Patient data were derived from the Clinical Practice Research Datalink (CPRD) linked to NHS Hospital Episode Statistics datasets.

Primary independent variable

Infection.

Primary and secondary outcome measures

The primary outcome was total inpatient costs from index stay admission through one-year of follow-up. Secondary outcome included cumulative total healthcare costs, and resource utilisation at 30 days, 90 days, 1 year and 2 years.

Results

Overall, 805 patients met the inclusion criteria. At index inpatient stay, 3.7% had a post IMN infection, rising to 11.7% at 1-year. One-year inpatient costs were 80% higher for patients with infection ($p<0.001$). Total costs were estimated to be £14,756 (95% confidence interval [CI]; £13,123, £16,593) for patients with infection versus £8,279 (95% CI; £7,946, £8,626). Length of stay (LOS), readmission, and reoperation were the key drivers of healthcare costs (all $p<0.001$). After adjustment, LOS was higher by 109% (95% CI: 62%, 169%), from 10.5 days to 21.9 days, for patients with infection. The odds of being readmitted or requiring reoperation were higher by 5.18 times (95% CI: 3.01, 9.13) and 2.47 times (95% CI: 1.48, 4.09), respectively, for patients with infection versus those without infection.

Conclusions

Post IMN infection significantly increases inpatient costs, LOS, readmissions, and reoperations associated with tibial fracture fixation. Healthcare burden could be reduced through novel surgical site infection prevention strategies.

Strengths and limitations of this study

- This is the first study to quantify the healthcare resource burden of infections following tibial shaft fractures treated with intramedullary nailing in England.
- The study had a long term and cross-sector perspective that included inpatient, hospital outpatient and primary care parameters.
- This study only considered patients with complete follow-up, thus excluding very severe patients with short life expectancy.
- Some costs were not directly available from the CPRD dataset and were sourced from published national sources.

- The study relied on clinical codes to identify superficial and deep infections which may be subject to coding errors and misclassifications.

Introduction

Tibial shaft fractures are the most common type of long-bone fracture. They can be either closed fractures, where the skin remains intact, or open fractures (accounting for 25% of all tibial shaft fractures) where the skin is broken (1).

Intramedullary nailing is a common surgical treatment for this type of injury. Infection after intramedullary nailing is a potential complication, especially in severe open fractures, that can delay wound healing and fracture repair (2-5). If left untreated, an infection may lead to permanent loss of function of the affected limb (2, 3, 6). Open fractures are especially prone to infection due to wound exposure to the environment with the risk of infection depending on the severity of soft tissue damage (4). Patients with cases of extreme and uncontrollable infection may require limb amputation to prevent deterioration and maintain quality of life (2).

Infections following fracture fixation are subclassified according to the depth of the infection: superficial (subcutaneous region), deep (muscle/fascial region), or organ/space infections (7). However, there is debate over the usefulness of these terms, as they can be arbitrary depending on the location of an infection (6). A US study reported an infection rate of 2% after intramedullary nailing for closed fractures compared with 7.1% for open fractures (8). A Belgian study reported an infection rate of 4.3% in patients with open or closed fractures, of which 1.4% were deep (9). In a meta-analysis of studies investigating prophylactic antibiotic use in patients with open tibial fractures treated with intramedullary nailing, the risk of infection increased with severity of the fracture, rising to over 31% among patients with the most severe injury (and who received systemic antibiotics only) (5).

Patients who experience infection are more likely to require additional surgeries, extended hospital stays, and extensive treatment for post-operative infection (2-4, 6). There are only a limited number of studies, however, which compare healthcare resource utilisation and treatment costs for tibial shaft fractures with and without post-surgical infection across Europe. In a Belgian study, healthcare costs were five times higher and total length of hospital stay (LOS) six times longer for open tibial shaft fracture patients with deep infection versus those with no infection (10). In Denmark, the average direct cost of treating a severe open tibial shaft fracture was estimated to be €49,817, increasing to €81,155 when infection occurred. In patients treated within 7 days of their injury, infection increased the average direct cost and LOS by 124% and 135%, respectively (11).

The aim of this nonconcurrent cohort study was to determine the impact of infections on healthcare costs and resource utilisation for patients undergoing intramedullary nailing for tibial shaft fractures from the perspective of National Health Service (NHS) England.

Materials and methods

Study design and setting

This was a nonconcurrent cohort study based on retrospectively collected data of patients in England who underwent intramedullary nailing for tibial shaft fracture (open or closed) and were followed-up for 2 years. Data derived from the Clinical Practice Research Datalink (CPRD) linked to NHS Hospital Episode Statistics (HES) and NHS Reference costs were used to calculate costs and healthcare resource utilisation associated with infections (superficial or deep) following intramedullary nailing.

The CPRD database is an anonymised longitudinal dataset of over 11.3 million medical records from over 600 primary care practices across the UK (12). It includes all visits to primary care and other healthcare professionals, reasons for visits, diagnoses observations, medical history,

test results, referrals, and prescriptions (12). For this study, HES data relating to admissions to, or attendances at, English NHS healthcare providers was used (HES Admitted Patient Care data).

Patients

The study population included adults (aged ≥18 years) who were diagnosed with an isolated or not tibial shaft fracture (ICD-10 code: S82.2) between May 2003 and June 2017 and who subsequently underwent intramedullary nailing within 30 days of diagnosis. Inclusion and exclusion criteria and patient attrition flow are depicted in Figure 1.

Infections were identified using clinical diagnosis codes either from the inpatient setting (ICD-10, OPCS codes) or the primary care setting (Read codes) (See Additional file 1). Only patients with an infection occurring on (or after) Day 2 following the index date were considered eligible for the infection cohort, as this would exclude infections that were present pre-operatively. For subgroup analysis, diagnosis codes were categorised into either deep or superficial infections and open or closed fractures based on medical knowledge.

Data collection

The primary outcome of this study was total inpatient costs (Healthcare Resource Group [HRG], unbundled HRG and specialised care) accrued beginning from index stay admission through one-year of follow-up post-discharge from the index stay. Secondary endpoints included cumulative total healthcare costs and resource utilisation for 30 days, 90 days, 1 year and 2 years of follow-up post discharge of the index stay. Total healthcare costs comprised inpatient, hospital outpatient and primary care costs (consisting of consultations, prescriptions, and tests/investigations). Healthcare resource utilisation included LOS, readmissions, reoperations, days in intensive care unit (ICU), hospital outpatient visits, diagnostic tests, and primary care visits. Time to infection was an additional secondary outcome.

Resource use and costs

Healthcare cost data were estimated based on the healthcare resource utilisation reported in CPRD/HES and the unit cost associated with each service from an NHS perspective. In England, NHS provides preventive medicine, primary care and hospital services to 88% of the citizens. Responsibility for publicly funded health care remains with the Secretary of State for Health, supported by the Department of Health (13). Hospitals are reimbursed by NHS according to the amount and type of activity that they perform using Healthcare Resource Groups (HRGs) (14).

Inpatient costs

The 2017/2018 HRG Reference Costs Grouper software was used to generate HRG codes for each inpatient admission (15, 16). Each HRG code was assigned an appropriate cost from NHS Reference Costs (17), using admission method, LOS, trim point and the patient classification to associate the relevant costs (15, 18, 19). Inpatient stays were considered as long-stays for admissions lasting ≥2 days in line with NHS reference costs (18, 20). Unbundled HRGs were automatically generated by the Grouper software and assigned relevant costs (17). Specialised care episodes were identified using the Prescribed Specialised Services Tool 2017/18 software and top-up costs were applied as a percentage increase to the HRG cost (21).

Hospital outpatient costs

Outpatient costs were derived from the CPRD referral file where the referral type was classified as “outpatient” and matched against NHS reference costs for the same or closest matching specialty (17, 19).

Primary care costs

Consultations from the CPRD consultations file were categorised based on the setting (clinical, surgery, home, telephone, administrative) and healthcare provider (doctor, nurse, other professional). Costs were sourced from the Unit Costs of Health and Social Care (22).

Laboratory and diagnostic tests from the CPRD tests file were manually matched to the closest NHS test category and assigned NHS Reference Costs (18).

Medication categories were based on British National Formulary classifications as recorded in the CPRD therapy file, and unit costs were obtained using the Prescription Cost Analysis 2017 using the mean sub-paragraph cost associated with each medication (23).

Follow-up period and cohort definitions

Follow-up time was calculated as the difference between the index discharge date and the last date of observation. Only patients with follow-up data at the relevant time point were included in the analysis.

Statistical analyses

All analyses were conducted using R Studio v3.4.3. Statistical significance was set a priori at $p<0.05$ (two-sided). Study variables were analysed descriptively. Time-to-infection was depicted graphically using the Kaplan-Meier estimator. Unadjusted comparisons of patient demographics, comorbidities, and medication use between groups were performed using t-tests for continuous variables that were approximately normal, and Wilcoxon rank sum tests for continuous variables that were not normally distributed. Pre-specified subgroup analyses allowed for stratification of results according to type of fracture (open versus closed) or type of infection (superficial versus deep).

Generalised Linear Models were used to adjust for confounding, to isolate the association between surgical site infection and the outcomes. Covariates were identified a priori as risk factors for the study outcomes based on clinical knowledge. A backwards stepwise procedure

was applied according to Akaike information criterion. Missing data were not imputed. Except for in the sensitivity analyses, patients with missing data were excluded from analyses.

Sensitivity analyses at all time points were conducted using data from the subgroup of patients who had complete two-year follow-up for total costs, LOS, readmission (rate and mean count), and reoperation (rate and mean count).

Patient and public Involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Results

Patient baseline characteristics

Of the 10,825 patients identified as having suffered a tibial shaft fracture, 3,005 received intramedullary nailing. Of these, a total of 805 patients met the inclusion criteria and were included in the study (Figure 1). The mean follow-up time was 4.8 years. The mean (standard deviation [SD]) age was 40.8 (17.2) (See Table 1 for index stay; Additional file 2). A majority of patients were male (n= 590; 73.3%) and most had suffered a closed (n=663; 82.4%) tibial shaft fracture. Among patients with an open fracture, a significantly higher proportion of patients (10.6%) experienced an infection compared with 2.3% of patients with a closed fracture (p<0.001; Table 1).

Figure 1. Patient screening and enrolment according to the study inclusion/exclusion criteria

Table 1. Patient demographic and clinical characteristics at index

	All enrolled patients (N=805)	Index stay		
		No infection (N=775)	Infection (N=30)	p-value
Demographics				
Age (years), mean (SD)	40.8 (17.2)	40.7 (16.8)	43.0 (23.9)	0.61
Gender, n (%) Male	590 (73.3)	569 (73.4)	21 (70.0)	0.84
Clinical history/comorbidities				
Charlson score, median (range)	0.00 (3.00)	0.00 (2.00)	0.00 (3.00)	<0.001
Smoker, n (%)	256 (31.8)	247 (31.9)	9 (30.0)	0.99
Diabetes, n (%)	27 (3.4)	27 (3.5)	0 (0.0)	0.62
COPD, n (%)	8 (1.0)	8 (1.0)	0 (0.0)	1.00
Congestive heart failure, n (%)	2 (0.3)	2 (0.3)	0 (0.0)	1.00
Hypertension, n (%)	12 (1.5)	12 (1.6)	0 (0.0)	1.00
Compartment syndrome, n (%)	27 (3.4)	22 (2.8)	5 (16.7)	<0.01
Index episode				
Inpatient waiting time (days) for surgery, mean (SD)	1.4 (2.4)	1.4 (2.4)	0.70 (2.4)	0.14
Fracture type, n (%) Open fracture	142 (17.6)	127 (16.4)	15 (50.0)	<0.001
Received ≥1 prescription for antibiotics in the 12 months prior to the index stay, n (%)	60 (7.5)	60 (7.7)	0 (0.00)	0.16
Received ≥1 prescription for opioids in the 12 months prior to the index stay, n (%)	16 (2.0)	15 (1.9)	1 (3.3)	0.46

Abbreviations: COPD, chronic obstructive pulmonary disease; SD, standard deviation.

Infection rates

During the index stay, 30 patients (3.7%) experienced an infection. Among patients with 30-day, 90-day, 1-year, and 2-years post-discharge follow-up data, infection rates were respectively: 8.0%, 9.2%, 11.7%, and 13.4%, (Figure 2).

Figure 2. Cumulative percentage of infection events recorded post-index date

One-year inpatient costs

Among patients with index stay plus 1-year post discharge data (N=686), the mean 1-year total inpatient cost was significantly higher among patients who experienced an infection (£15,580;

n=80) compared with patients without infection (£7,746; p<0.001). After adjusting for fracture type (open/closed), age, smoking status, index year, diabetes, COPD, inpatient waiting time for surgery and compartment syndrome, mean costs were 80% (95% CI: 58%, 104%) higher, respectively (£13,672 [95% CI: £12,122, £15,420] versus £7,616 [95% CI: £7,301, £7,944]; p<0.001), (Figure 3).

One-year total costs

Adjusted total costs were £14,756 (95% CI: £13,123, £16,593) among patients who experienced an infection versus £8,279 (95% CI: £7,946, £8,626; p<0.001) in patients without infection – a 78% increase in total costs as a result of infection (95% CI: 57%, 102%) (Figure 3).

Figure 3. Breakdown of 1-year total costs by infection status (adjusted analysis)

Abbreviations: ns, not significant; CI, confidence interval.

*** p<0.001

One-year healthcare resource use

For the majority of healthcare resource categories, presence of infection was associated with a statistically significant increase in resource use versus no infection (Table 2). Key drivers of increased costs were LOS, readmission, and reoperation rates, which were all significantly higher in patients with infections (all p<0.001). After adjustment, LOS was increased by 109% (95% CI: 62%, 169%) from 10.5 days to 21.9 days. The odds of being readmitted or requiring reoperation due to infection was increased by 5.18 times (95% CI: 3.01, 9.13) and 2.47 times (95% CI: 1.48, 4.09), respectively.

Table 2. 1-year healthcare resource use by infection status

	Multivariate analysis		
	No infection (N=606) Mean (95% CI)	**Infection N=80 Mean (95% CI)**	**p-value**
LOS, days	10.5 (9.7, 11.4)	21.9 (17.3, 27.7)	p<0.001

	Multivariate analysis		
	No infection (N=606) Mean (95% CI)	**Infection N=80 Mean (95% CI)**	**p-value**
ICU LOS, days	0.01 (0.01, 0.02)	0.01 (0.00, 0.02)	p=0.91
Number of readmissions	0.5 (0.5, 0.6)	1.5 (1.2, 1.8)	p<0.001
Readmission rate, %	35.9 (32.1, 39.9)	74.4 (63.4, 83.0)	p<0.001
Number of reoperations	0.2 (0.2, 0.3)	0.6 (0.5, 0.8)	p<0.001
Reoperations rate, %	20.3 (17.2, 23.8)	38.6 (28.3, 50.0)	p<0.001
Number of hospital outpatient referrals	1.8 (1.6, 2.1)	1.7 (1.2, 2.1)	p=0.44
Primary care resource use			
Number of primary care events	30.9 (29.2, 32.7)	45.9 (39.0, 54.0)	p<0.001
Number of tests and examinations	14.0 (11.4, 16.6)	22.1 (13.9, 31.3)	p=0.052

Abbreviations: CI, confidence interval; ICU, intensive care unit; LOS, length of stay

Total costs from index stay to two years follow-up

At all-time points mean total costs were statistically significantly higher for patients with an infection compared with those without (p<0.001), (Figure 4). Adjusted mean total costs of care in patients with infection versus no infection over time were: £11,257 versus £7,017 at 30 days; £11,949 versus £7,423 at 90 days; and £16,626 versus £9,439 at 2 years (all p<0.001).

Figure 4. Total costs from index stay to 2 years follow-up

Abbreviations: CI, confidence interval.

*** p<0.001. Data plotted are means +/- 95% CI.

Healthcare resource use from index stay to two years follow-up

Multivariate analysis demonstrated that LOS, readmissions (rate and mean; Figure 5), and reoperations (rate and mean; Figure 6), were consistently higher at all timepoints among patients who experienced an infection compared with those who did not (p<0.001). At 30 days, infection increased the adjusted LOS from 8.9 days to 15.0 days and at 2 years from 11.3 days to 24.6 days (both p<0.001). The adjusted readmission rate increased from 7.1% at 30 days to 51.3% at 2 years follow-up in patients without infection compared with an increase from 44.1%

to 77.6% in the infection group (Figure 5). The adjusted reoperation rate increased from 1.3% at 30 days to 31.2% at 2 years in the absence of infection, whereas in the infection group, the rate increased from 11.5% to 49.0% (Figure 6).

Figure 5. Readmission (adjusted) according to follow-up time: (A) readmission rate and (B) mean number of readmissions per patient

Abbreviations: CI, confidence interval.

*** p<0.001. Data plotted are means +/- 95% CI.

Figure 6. Reoperation (adjusted) according to follow-up time: (A) reoperation rate and (B) mean number of reoperations per patient

Abbreviations: CI, confidence interval.

** p<0.01, *** p<0.001. Data plotted are means +/- 95% CI.

Subgroup analyses

Multivariate analysis by infection type resulted in mean 1-year inpatient costs of £7,614, £12,814 and £15,513, respectively for no infection (n=606), superficial infection (n=54) and deep infection (n=26) (Additional file 2). Analysis by fracture type showed a higher 1-year infection rate among patients with open fractures (27.4%) versus closed fractures (8.6%). Mean adjusted inpatient costs at 1 year for patients with and without infection were £19,542 versus £9,495 for patients with open fractures and £12,178 versus £7,278 for patients with closed fractures.

Sensitivity analyses

A total of 588 patients (73%) out of the 805 patients at index had data for the full 2-year follow-up period. Results for total costs, LOS, readmissions (rate and mean), and reoperations (rate

and mean) at each time point were consistent with those of the primary analyses (Additional file 2).

Discussion

This study used CPRD-linked HES data to determine the impact of infection on English healthcare costs and resource utilisation associated with patients undergoing intramedullary nailing for tibial fracture. Infection rates at 1-year and 2-years (11.7% and 13.4%, respectively) were comparable with the 10.5% rate reported in a 2014 meta-analysis (5). Mean inpatient costs measured after 1 year were predicted to be 80% higher (£6,056) for patients with infection compared with those without infection, while overall costs were 78% higher. The greatest cost drivers were hospital LOS (109% increase at 1 year), readmissions (odds of being readmitted increased by 5.18 times at 1 year), and reoperations (odds of reoperation increased by 2.47 times at 1 year). The 2-year follow-up in this study meant that we were able to capture changes in resource use over time associated with infection, such as readmission and reoperation. The findings of this study highlight the substantial impact on healthcare resource utilisation and costs to the English NHS, from both the hospital and primary care perspective.

This study is the first to quantify the additional healthcare resource burden of infections following tibial fractures treated with intramedullary nailing in England with a long-term perspective which includes inpatient, hospital outpatient and primary care parameters. Differences in healthcare systems, patient populations and treatment pathways make direct comparison with studies from other countries challenging; however, our findings are in line with results of studies from Belgium and Denmark (10, 11). Hoekstra et al. demonstrated five times higher healthcare costs and six times longer LOS for open tibial shaft fracture patients with deep infection versus those without infection in Belgium (10). Although the magnitude of the increase in costs and LOS observed in our study is not as substantial, differences in patient populations may be a contributing factor, as Hoekstra et al. did not limit their study population to intramedullary nail

fixation (10). In their Danish study, Olesen et al. estimated a 60% increase in direct costs and an 80% increase in LOS resulting from infected open tibial fractures (11), consistent with the magnitude of the increase observed in the current study; absolute LOS (74 days) and direct healthcare costs (€81,155) in the presence of infection were substantially higher than in our study, however, which may in part reflect the most severe types of wounds considered in the Danish study, all of which were open fractures and 80% of which were Gustilo-Anderson classification 3. Furthermore, a US-study found that surgical site infections nearly doubled inpatient costs to $109,000 in patients with isolated fractures (24).

Surgical site infections remain one of the most challenging complications in trauma surgery (25). Over the past decades, surgical site infection incidence has decreased, especially deep infections in patients with open tibial fractures (26). The question remained whether these rates could be decreased further. Still, no infections occurred in two studies in complex tibial fracture patients treated with antibiotic coated intramedullary tibia nails (27, 28). Based on consensus opinions, they may be a promising option for prevention of surgical site infections in open fractures or revision cases (29). Other approaches to prevent infections through local delivery of antibacterials were based on specialized biomaterials formulated as additives in bone void fillers such as bone cement or bacteriostatic bone substitute materials (25, 30, 31). Moreover, in order to prevent infections, open fractures should be managed according to the UK NICE guideline and the Open fracture BOAST (32, 33).

This study is subject to the following limitations: 1) potential bias in the patient population as we only considered patients with complete follow-up, thus excluding very severe patients with short life expectancy or with few comorbidities, limiting the generalizability of the findings to this subgroup; 2) identification of relevant patients for inclusion in the study was based on OPCS, ICD-10 and primary care-based read codes. The data may be susceptible to coding errors and misclassifications. Surgical site infections were defined following the CDC criteria (34, 35).

Recently it became clear that the CDC definition for infection probably is not sufficient to define fracture-related infections. One important reason is the fact that the subdivision of infection into superficial and deep infection is arbitrary (36). However, the use of the CDC definition was standard during our study period (2003 – 2017); 3) medication use was costed as recorded in CPRD , i.e. averaged to the cost of the drug family/British National Formulary sub-paragraph; 4) dispensing costs were not included 5) outpatient specialties from CPRD did not always exactly match outpatient specialty categories from NHS Reference Costs; when there was not an exact match, the closest matching specialty was chosen; 6) costs were not directly available from the CPRD dataset and hence unit costs had to be sourced from published national sources for primary and secondary care and for drug prices; 7) economic assessment was limited to direct healthcare costs while infections could lead to permanent functional loss and potentially increase in secondary costs (25); 8) all potential confounders could not be adjusted for, limiting the association between increased healthcare resource utilizations and costs with surgical site infections.

Our study provides important evidence as to the short- to mid-term direct economic consequences of infection following tibial fractures. By increasing the sample size, the impact of infection type (superficial/deep) and fracture type (open/closed) could have been explored more robustly. Additional validation of clinical codes used to identify relevant data would have allowed us to account for any potential variation in clinical coding practice. Broadening the perspective to include indirect costs would allow the additional burden of infection to be established, such as rehabilitation and absenteeism.

Conclusion

This study confirms that infection presents a substantial healthcare burden, leading to significantly increased hospital LOS, need for hospital readmission and reoperation, and increased use of GPs and other primary care resources. As such there exists an unmet need for

alternative medical technologies and infection prevention strategies that could help to reduce infections in tibial shaft fractures and reduce costs. Our study indicates that the potential mid-term (1–2 years) saving to the English NHS of is around £6,500 per patient.

Declarations

Ethics approval and consent to participate

The study protocol was approved by the Independent Scientific Advisory Committee for Medicines and Healthcare products Regulatory Agency database research (ISAC) on 27 November 2017 (ISAC Protocol: 17-132R). General ethical approval for observational research using the CPRD with approval from the ISAC was granted by a Health Research Authority Research Ethics Committee (East Midlands – Derby; reference number: 05/MRE04/87).

Consent for publication

Not applicable

Availability of data and material

The data that support the findings of this study are available from Clinical Practice Research Datalink (CPRD), but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available.

Competing interests

Peter Giannoudis received honoraria from DePuy Synthes for his involvement in this study. Thibaut Galvain, Abhishek Chitnis, Cindy Tong, and Chantal Holy are employees of Johnson and Johnson Medical Devices. Konstantina Paparouni is an employee of DePuy Synthes. The funding corporations could have affected the study design, analysis and manuscript writing; but authors owned final decisions.

Funding

This study was sponsored by DePuy Synthes.

Authors' contributions

Study conception and design: TG, PVG, CEH, KP, CT and AC. Acquisition of data: TG, PVG, CT and AC. Data analysis: TG, CT and AC. Interpretation of data and results: TG, PVG, CEH, KP, CT and AC. Drafting of manuscript: TG, PVG, CEH, KP, CT and AC. Critical revision: TG, PVG, CEH, KP, CT and AC. Project management: KP.

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Abbreviations

BOAST, British Orthopaedic Association Standards for Trauma & Orthopaedic; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CPRD, Clinical Practice Research Datalink; GP, general practitioner; HES, Hospital Episode Statistics; HRG, Healthcare Resource Group; ICU, intensive care unit; ISAC, Independent Scientific Advisory Committee; LOS, length of stay; NA, not applicable; NICE, National Institute for Health and Care Excellence; NHS, National Health Service; SD, standard deviation.

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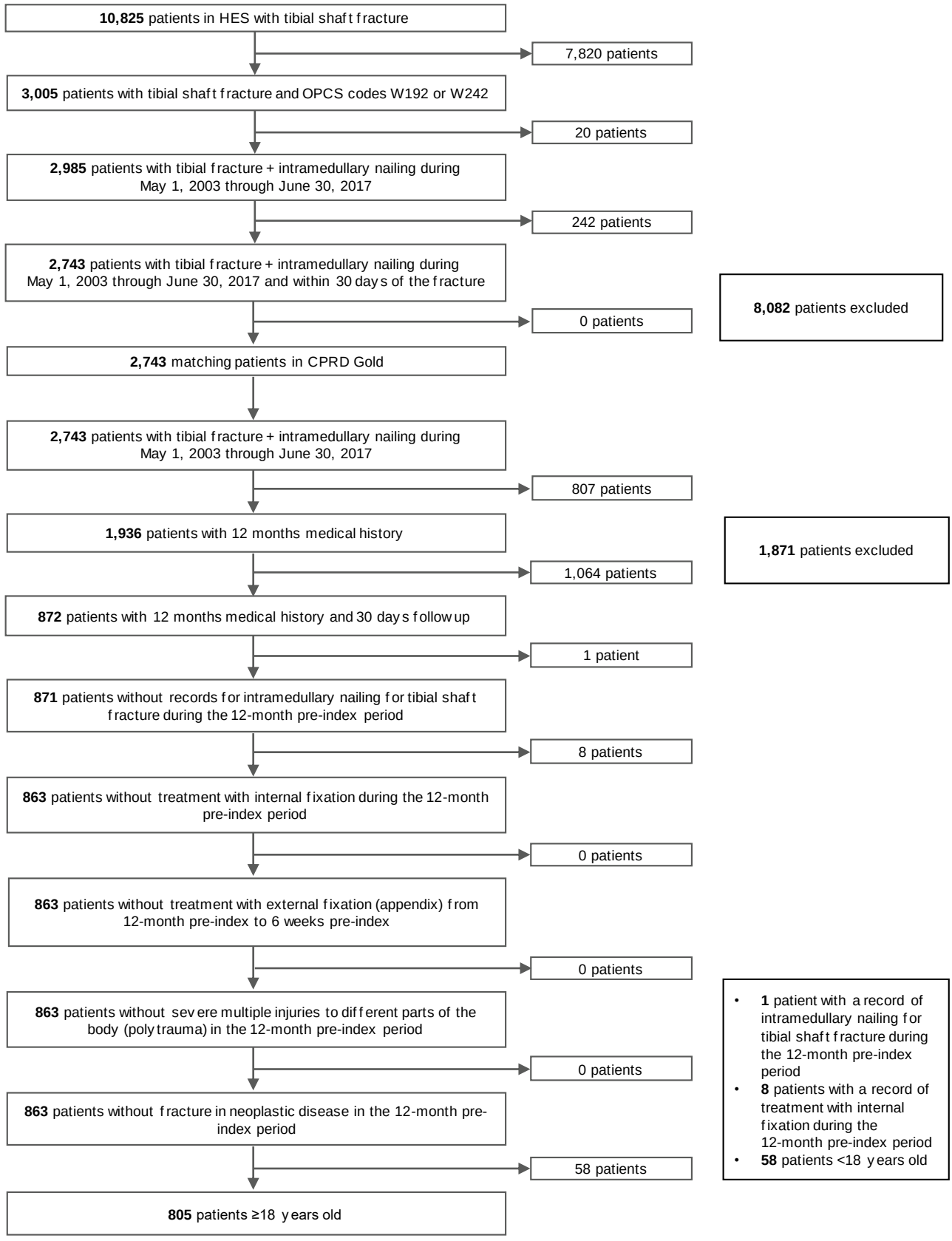
Additional files

1. Additional file 1:
    a. Format: “Additional file1.pdf”
    b. Title: Study protocol
    c. Description: this additional file includes the study protocol and its appendix composed of clinical and procedure codes
2. Additional file 2:
    a. Format: “Additional file2.pdf”
    b. Title: Baseline and results at all time points
    c. Description: this additional file includes the baseline demographics and results at all time points that could not be integrated in the manuscript.



Final cohort
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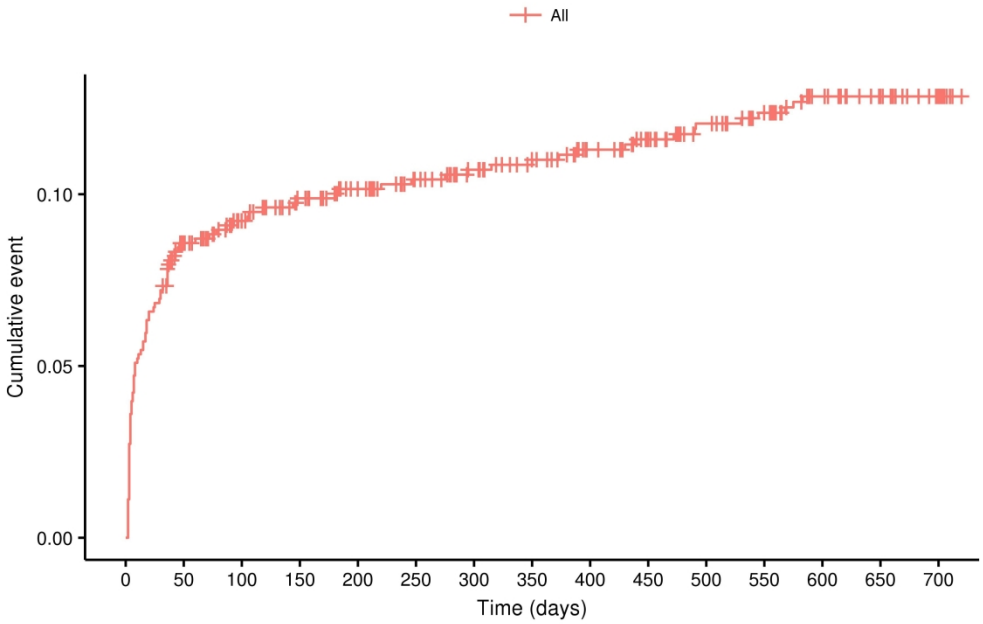

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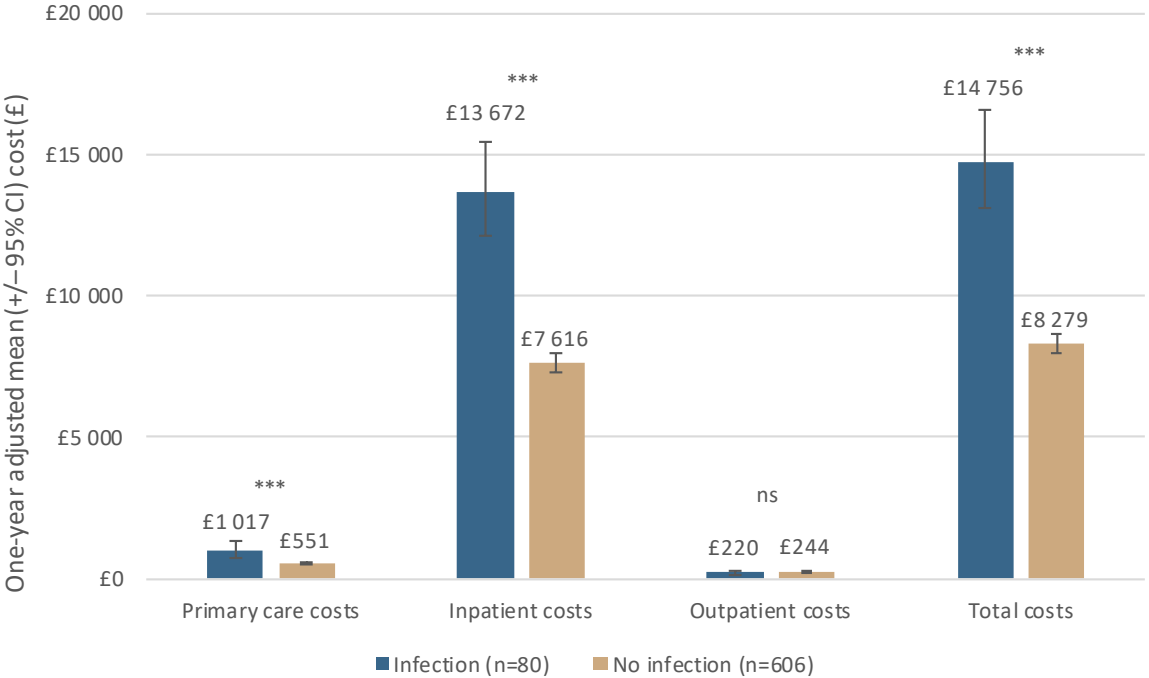
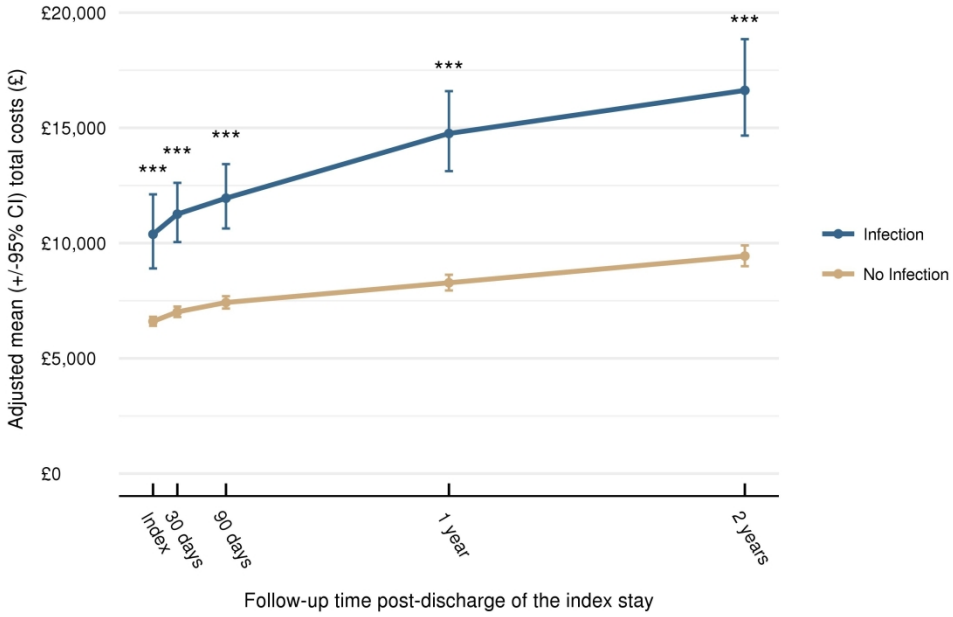




Abbreviations: CI, confidence interval. *** p<0.001. Data plotted are means +/- 95% CI.

152x101mm (600 x 600 DPI)

Figure 5A

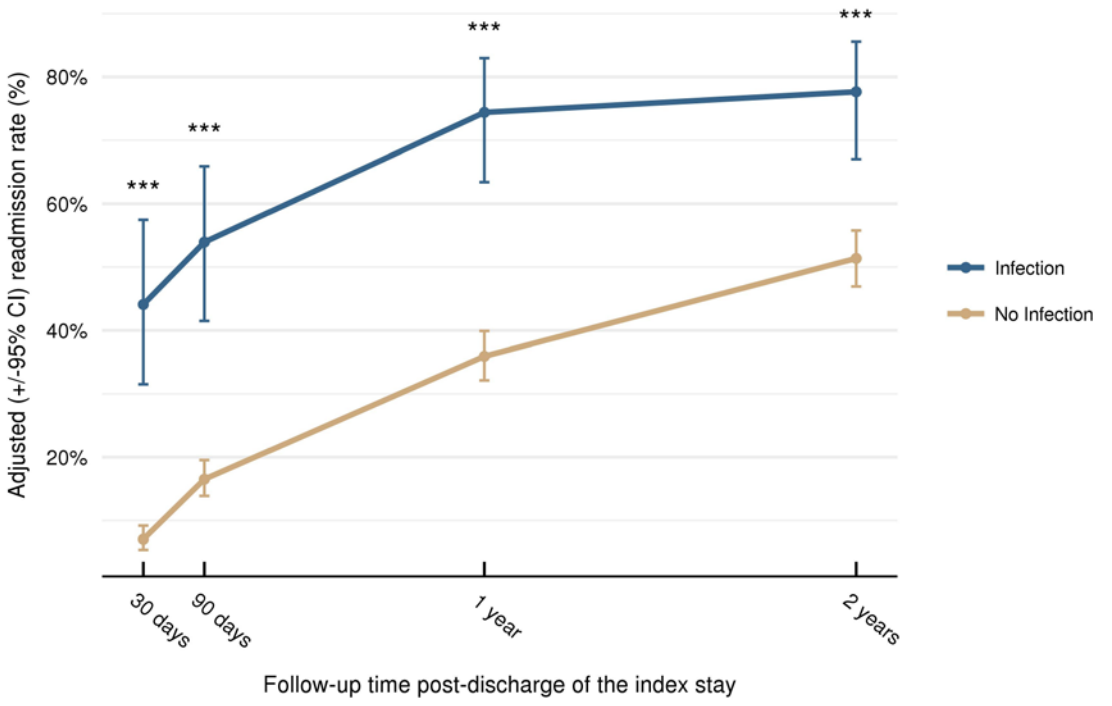


Figure 5B

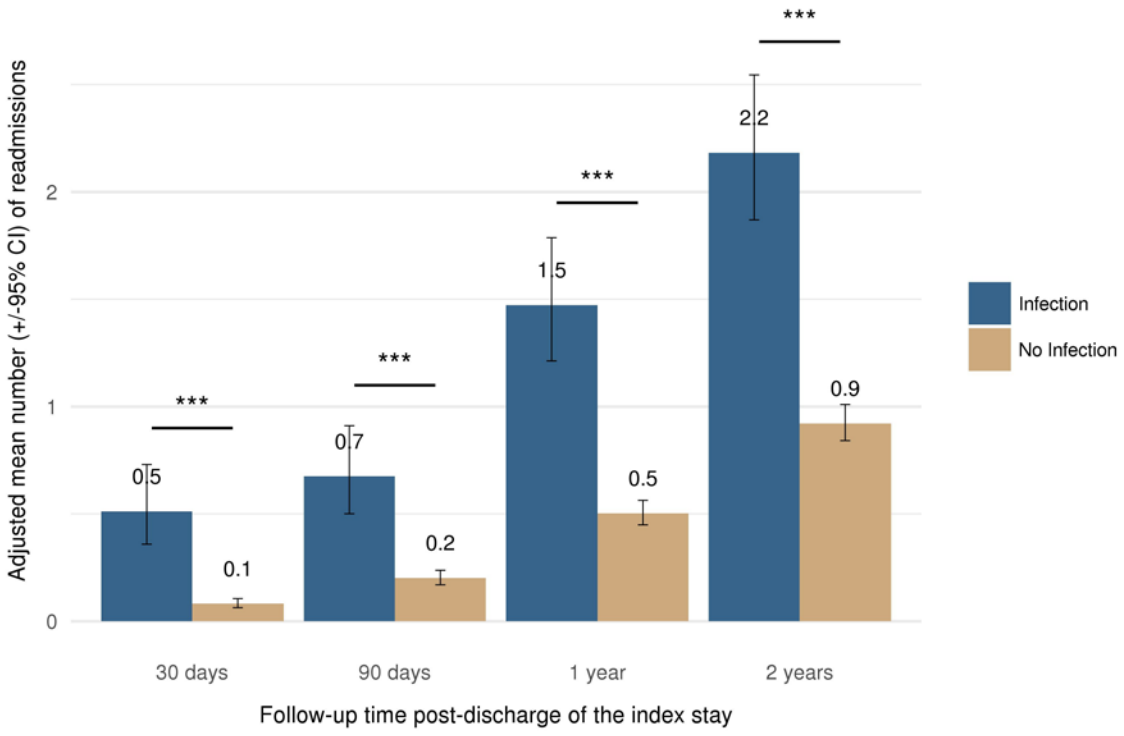


Figure 6A

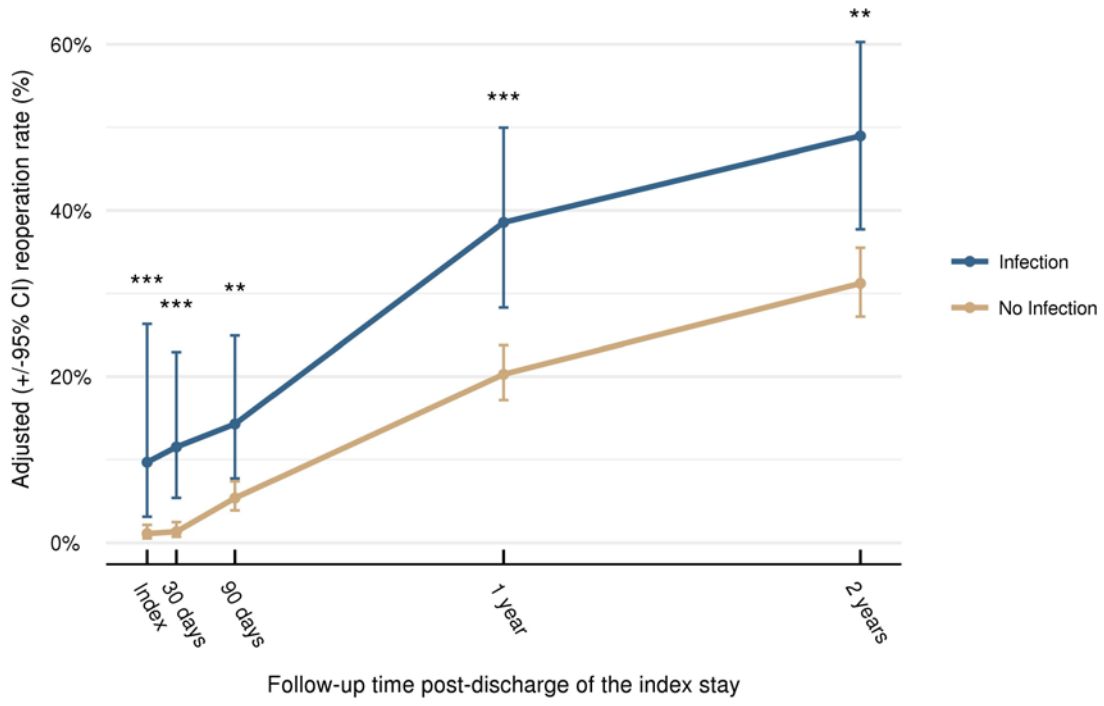
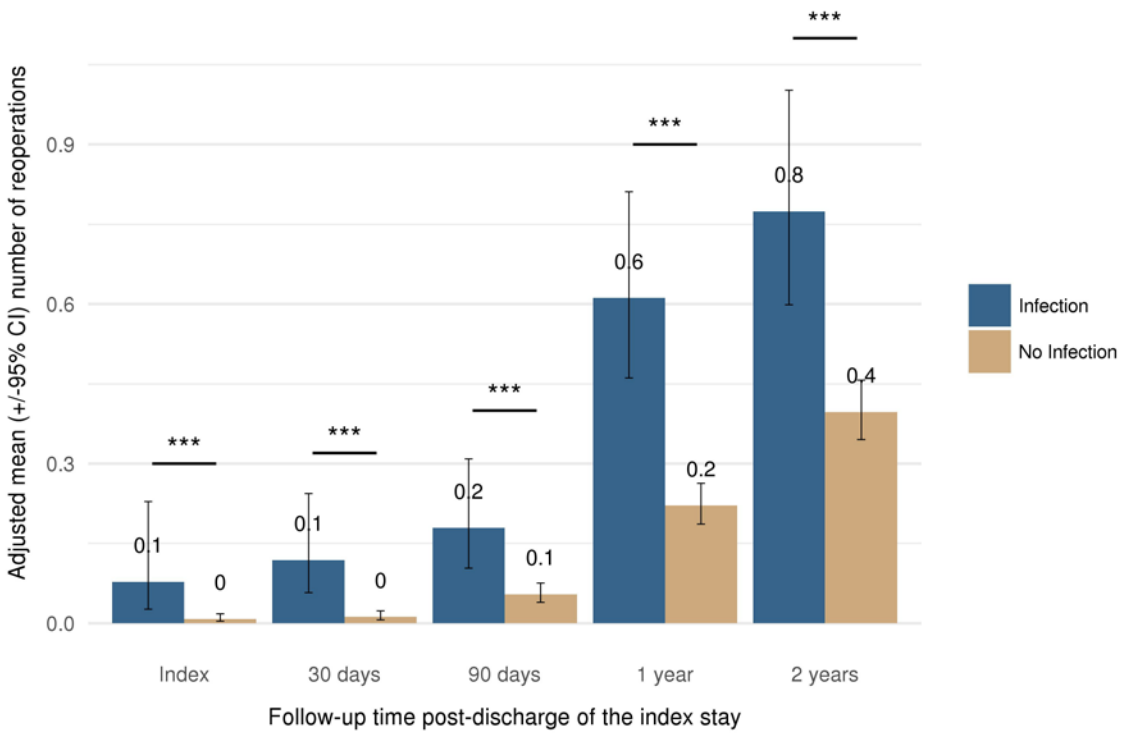


Figure 6B



Additional file 1: Study protocol

PROTOCOL INFORMATION REQUIRED

The following sections below **must** be included in the CPRD ISAC research protocol. Please refer to the guidance on '***Contents of CPRD ISAC Research Protocols***' (www.cprd.com/isac) for more information on how to complete the sections below. Pages should be numbered. All abbreviations must be defined on first use.

Applicants must complete all sections listed below **Sections which do not apply should be completed as '*Not Applicable*'**
A. Study Title[§] [§]*Please note: This information will be published on CPRD's website as part of its transparency policy* Healthcare Resource Utilization and Costs among Patients with and without Infection after Intramedullary Nailing for A Tibial Shaft Fracture
B. Lay Summary (Max. 200 words)[§] [§]*Please note: This information will be published on CPRD's website as part of its transparency policy* Tibial shaft fractures are the most common long bone fracture of the lower limbs. Intramedullary nailing is the most frequent surgical treatment for tibial shaft fractures. In patients with tibial shaft fractures, infection is an important complication as about 15% of these fractures are open injuries. Such infections may lead to devastating consequences such as increase in length of hospital stay, readmissions, prolonged medication treatment and reoperations along with high use of medical resources and costs. However, the healthcare burden among patients developing an infection in tibial shaft fracture is not well documented. Consequently, this study seeks to understand the impact of infection after intramedullary nailing in patients with tibial shaft fractures on healthcare use and cost of care.
C. Technical Summary (Max. 200 words)[§] [§]*Please note: This information will be published on CPRD's website as part of its transparency policy* The objective of this retrospective longitudinal cohort study is primarily designed to determine short (30-day, 90-day) and mid-term (one-year, two-year) healthcare resource utilization (HRU) and costs among patients with deep and superficial infections versus those without following intramedullary nailing for a tibial shaft fracture. Patients with tibial shaft fracture treated with intramedullary nailing between 2011 and 2016 will be selected. The main exposure variable will include deep infection versus superficial surgical site infection or no infection. Analyses will be both descriptive and comparative using multivariable models. The multivariable models will include generalized linear models (GLMs) based on the outcome variable of interest for HRU and costs and will adjust for patient characteristics.

Applicants must complete all sections listed below
Sections which do not apply should be completed as '*Not Applicable*'

D. Objectives, Specific Aims and Rationale

Broad Research Objectives

To evaluate the impact of developing infection in patients with intramedullary nailing for tibial shaft fractures on healthcare utilization and cost of care.

Specific Aims

1. To determine short (30-day, 90-day) and mid-term (one-year, two-year) Costs and HRU among patients with deep infection and superficial infections versus patients without an infection following tibial shaft fracture treated with nailing.

Rationale

This study seeks to understand the impact of post-surgical infection in patients with intramedullary nailing for tibial shaft fractures on cost of care and healthcare utilization.

E. Study Background

Infections remains a feared complication in orthopaedic and trauma surgery due to its potentially devastating consequences for patients. It has also been associated with an increase in medical resource utilization and treatment costs due to increased length of hospital stay, readmissions, prolonged pharmacological treatment and reoperations. [1-6] Deep infections defined as infections involving deeper tissues such as muscular fascia and bone[7] have been associated with a significant economic burden for healthcare systems. Data from long bone fracture reduction, hip replacement or hemiarthroplasty or screw fixation for proximal humeral fractures and knee arthroplasty, consistently reported 2-3 times higher treatment costs for patients that developed an infection compared to those that did not. [1-6]

Tibial shaft fractures are the most common long bone fracture of the lower limbs.[8] In patients with tibial shaft fractures, infection is an important complication as about 15% of these fractures are open injuries. Infection may lead to prolonged treatment, compromised clinical outcomes and in some cases, even limb amputation. [9-12] In the European setting there is limited data available with respect to the actual cost of treatment. In a Danish study on patients with open tibia fractures treated with a free flap , the presence of an infection increased the mean length of hospital stay from 28 to 63.8 days and the mean treatment costs from €49,301 to €67,958 for infected compared to uninfected fractures.[13]A study from the UK reported the mean length of stay and treatment costs of patients with tibial osteomyelitis. For patients treated with limb salvage procedures alone, length of stay was 15 days (10-27) and corresponding treatment costs were € 16,718 while for patients, whose treatment ended up in amputation length of stay was 13 days (8-17) and treatment costs were €18,441.[14]

Intramedullary nailing is the preferred surgical treatment in patients with tibial shaft fractures. The impact of the development of an infection on short and mid-term post-operative medical resource utilization is not well documented. While literature from clinical trials provides some insight into infection incidence rates, the treatment pathway and treatment success/failure rates, there is a lack of detailed patient-level information particularly in relation to the actual costs of care.

Applicants must complete all sections listed below Sections which do not apply should be completed as '*Not Applicable*'
F. Study Type Hypothesis generating This study will generate the hypothesis for HRU and costs between patients with (deep and superficial) and without infection after intramedullary nailing for tibial shaft fractures
G. Study Design This is a retrospective cohort study with a longitudinal follow-up for up to two years post intramedullary nailing for tibial shaft fractures.
H. Feasibility counts Based on the preliminary feasibility study of Hospital Episode Statistics (HES) inpatient data for research grade patients with complete data, we identified a total of 11,329 patients with intramedullary nailing for a tibial shaft fracture between 2011 and 2013 of which 509 patients had an infection following intramedullary nailing for a tibial shaft fracture.
I. Sample size considerations No prior real-world studies have been conducted to evaluate the health care resource use and costs of interest among patients with and without infection following intramedullary nailing for tibial shaft fracture. Therefore, it is not possible to estimate the sample size
J. Data Linkage Required (if applicable):[§] [§]*Please note that the data linkage/s requested in research protocols will be published by the CPRD as part of its transparency policy* The Clinical Practice Research Datalink (CPRD) with HES is required to identify the patients and outcomes that are based on diagnosis and procedures recorded in the inpatient setting.
K. Study population Patients initially selected for tibial shaft fracture (ICD-10, S822) must meet all the following inclusion criteria: 1. Procedure for intramedullary nailing for tibial shaft fracture (appendix) between January 1, 2011 and February 30, 2016 • Date of first intramedullary nailing for tibial shaft fracture between January 2011 and February 2016 will be the index date 2. Research grade patients with complete medical records for at least 12 months pre- and 30- day post index date. Patients with 90-day, 1- and 2- year follow-up or continuous enrollment will be further analysed. **Patients with the following criteria were excluded:** 1. Records for intramedullary nailing for tibial shaft fracture during the 12-month pre-index period 2. Records for treatment with internal fixation (appendix) during the 12-month pre-index period

Applicants must complete all sections listed below
Sections which do not apply should be completed as '*Not Applicable*'

3. Records for treatment with external fixation (appendix) from 12-month pre-index to 6 weeks pre-index. Records for external fixation during 6 weeks pre-index will be included as external fixation is often performed prior to intramedullary nailing.
4. Records for severe multiple injuries to different parts of the body (polytrauma) (appendix) in the 12-month pre-index period.
5. Records for a fracture in neoplastic disease (appendix) in the 12-month pre-index period.

L. Selection of comparison group(s) or controls

Patients not developing an infection anytime during the study period will be selected as the control group.

M. Exposures, Health Outcomes[§] and Covariates

[§]*Please note: Summary information on health outcomes (as included on the ISAC application form above)will be published on CPRD's website as part of its transparency policy*

Exposure

Patients developing infection during the 12-month post index period.

Outcome(s)

Primary Outcome

One- year inpatient costs

Secondary Outcomes

- Number of hospital readmissions (in 30-days, 90-days, 1 year and 2 years)
- Percent (yes/no) of patients with readmissions (in 30-days, 90-days, 1 year and 2 years)
- Total cost of care at the different time points (in 30-days, 90-days, 1 year and 2 years)
    a. Inpatient admissions
    b. Outpatient costs
    c. Pharmacy

Costs will be expressed in UK pounds and adjusted for inflation to 2015 index. Healthcare costs will be obtained from the Personal Social Services Research Unit (PSSRU) 2015 Cost of Care public document and Healthcare Resource Group (HRG) codes available in HES. Drug costs will be obtained from British National Formulary 71 (March 2016-September 2016).

- Number of procedures for introduction of therapeutic substance (Appendix) (30-days, 90-days, 1 year and 2 years)
- Number of outpatient visits (all-cause) at the different time points (in 30-days, 90-days, 1 year and 2 years)
- Number of diagnostic tests and imaging (all-cause) at the different time points (in 30-days, 90-days, 1 year and 2 years)
- Number of days in ICU (all-cause) at the different time points (in 30-days, 90-days, 1 year and 2 years)
- Time of infection and type of infection (bacterial vs other)

Applicants must complete all sections listed below
Sections which do not apply should be completed as '*Not Applicable*'

- Percent (yes/no) of patients with use of antibiotics at the different time points (in 30-days, 90-days, 1 year and 2 years)
- Patients necessitated amputation (Appendix) at the different time points (in 30-days, 90-days, 1 year and 2 years)

Covariates

The covariates information will be captured during 12-month pre-index period and will include the following:

Patient Demographics

- Age
- Gender
- Smoking status

Procedural Characteristics

- Year of the index date

Patient Clinical Characteristics

Comorbidities (Appendix)

- Diabetes
- Dyspnea
- Ventilator requirement
- Chronic obstructive pulmonary disease (COPD)
- Congestive heart failure (CHF)
- Renal failure
- Hypertension

Indices

- Charlson comorbidity index (CCI) - The CCI is an aggregate measure of comorbidity created by using select diagnoses associated with chronic disease (e.g., heart disease, cancer). The CCI includes 17 medical conditions and weights these conditions from +1 to +6.

Medications

- Anti-hypertensive medications
- Opioids

N. Data/ Statistical Analysis

All study variables will be analyzed descriptively. Frequency counts and proportions will be provided for dichotomous and polychotomous variables. Means, medians, and standard deviations will be provided for continuous variables. Time to infection will be depicted graphically using Kaplan-Meier curve.

Unadjusted comparisons of patient demographics, comorbidities and medication use between groups (with and without infection) will be performed with 2-sample t-tests for continuous variables and $\chi 2$ tests for categorical variables and Wilcoxon rank sum tests for cost variables.

Applicants must complete all sections listed below Sections which do not apply should be completed as '*Not Applicable*'
A sub-analysis will be conducted in which patients will be stratified by an open fracture and a closed tibial shaft fracture (appendix) to determine the outcomes. All analyses will be conducted using SAS for Windows. Statistical significance will be set a-priori at p< 0.05 (two-sided). In addition, a generalized Linear Model (GLM) will be utilized to get adjusted results after control for confounding. Details of this methods are mentioned in the section below:
O. Plan for addressing confounding Multivariable models will be constructed to examine the impact of infection versus no infection and other patient characteristics for healthcare utilization and cost outcomes. A Generalized Linear Model (GLM) will be utilized and the appropriate error distribution and link function will be used based on the outcome variable of interest for utilization and costs. Following standard procedures, for each model regression diagnostics will be performed to assess goodness of fit and violations of model assumptions. Appropriate modifications will be made as needed either through selection of alternative error distributions or link functions, or through transformations of either the independent or dependent variables. We will also examine the fitted and the observed data to uncover outliers, their effect on the analysis, and possible misspecification of the initial equation.
P. Plans for addressing missing data Missing data will not be imputed for the analyses. Most variables (drugs, procedures, diagnosis) can have no missing values, as they are assumed not to have occurred unless a record is identified. To be included in the study, patients will need to have complete medical history for at least 12 months pre-index to 12 months post-index date.
Q. Patient or user group involvement (if applicable) This is purely an observational study using CPRD with HES linkage data. This study does not involve requesting additional information from GPs. Also, the study does not require contacting patients to get any additional information.
R. Plans for disseminating and communicating study results, including the presence or absence of any restrictions on the extent and timing of publication The study will be disseminated per the ICMJE guidelines. We plan on submitting the results to a peer-reviewed journal and presenting the results at scientific conferences.
S. Limitations of the study design, data sources, and analytic methods

Applicants must complete all sections listed below
Sections which do not apply should be completed as '*Not Applicable*'

- Potential bias in patient population: only patients with complete medical history for 12 months post index will be included, thus excluding very severe patients with less than 12 month life expectancy
- Coding errors and misclassifications
- Under-reported or missing diagnoses, based on patients' choice (not to seek care) or access challenges
- Identify pharmacy cost in terms of medication prescribed in the primary care setting only
- Cost evaluated using PSSRU, HRG and BNF codes as the costs are not directly available in the data

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List of Appendices *(Submit all appendices as separate documents to this application)*

Applicants must complete all sections listed below
Sections which do not apply should be completed as '*Not Applicable*'

1. OPCS-4 codes to identify intramedullary nailing for long bones

OPCS-4	Description
W192	Primary open reduction of fracture of long bone and fixation using rigid nail NEC
W242	Closed reduction of fracture of long bone and rigid internal fixation NEC

2. OPCS-4 codes to identify internal fixation

OPCS-4	Description
O172	Remanipulation of fracture of long bone and rigid internal fixation NEC
O173	Remanipulation of fracture of long bone and flexible internal fixation HFQ
O175	Remanipulation of fragment of bone and fixation using screw
O178	Other specified secondary closed reduction of fracture of bone and internal fixation
O179	Unspecified secondary closed reduction of fracture of bone and internal fixation
W195	Primary open reduction of fragment of bone and fixation using screw
W196	Primary open reduction of fragment of bone and fixation using wire system
W198	Other specified primary open reduction of fracture of bone and intramedullary fixation
W199	Unspecified primary open reduction of fracture of bone and intramedullary fixation

OPCS-4	Description
W201	Primary open reduction of fracture of long bone and extramedullary fixation using plate NEC
W202	Primary open reduction of fracture of long bone and extramedullary fixation using cerclage
W203	Primary open reduction of fracture of long bone and extramedullary fixation using suture
W204	Primary open reduction of fracture of long bone and complex extramedullary fixation NEC
W208	Other specified primary open reduction of fracture of bone and extramedullary fixation
W209	Unspecified primary open reduction of fracture of bone and extramedullary fixation
W231	Secondary open reduction of fracture of bone and intramedullary fixation HFQ
W232	Secondary open reduction of fracture of bone and extramedullary fixation HFQ
W236	Secondary open reduction of fracture of bone and internal fixation HFQ
W248	Other specified closed reduction of fracture of bone and internal fixation
W249	Unspecified closed reduction of fracture of bone and internal fixation
W281	Application of internal fixation to bone NEC
W282	Adjustment to internal fixation of bone NEC
W283	Removal of internal fixation from bone NEC
W288	Other specified other internal fixation of bone
W289	Unspecified other internal fixation of bone

3. OPCS-4 codes to identify external fixation

OPCS-4	Description
W222	Primary open reduction of fracture of bone and external fixation HFQ
W235	Secondary open reduction of fracture of bone and external fixation HFQ
W252	Closed reduction of fracture of bone and fixation using functional bracing system
W253	Remanipulation of fracture of bone and external fixation HFQ
W258	Other specified closed reduction of fracture of bone and external fixation
W259	Unspecified closed reduction of fracture of bone and external fixation
W301	Application of external fixation to bone NEC
W302	Adjustment to external fixation of bone NEC
W303	Removal of external fixation from bone NEC
W304	Application of external ring fixation to bone NEC
W308	Other specified other external fixation of bone
W309	Unspecified other external fixation of bone

4. ICD-10 codes to identify severe multiple injuries

ICD-10 codes	Description
S097	Multiple injuries of head
S197	Multiple injuries of neck
S277	Multiple injuries of intrathoracic organs
S297	Multiple injuries of thorax
S397	Other multiple injuries of abdomen, lower back and pelvis
S497	Multiple injuries of shoulder and upper arm
S597	Multiple injuries of forearm
S647	Injury of multiple nerves at wrist and hand level
S697	Multiple injuries of wrist and hand
S797	Multiple injuries of hip and thigh
S897	Multiple injuries of lower leg
S997	Multiple injuries of ankle and foot
T042	Crushing injuries involving multiple region of upper limb(s)
T043	Crushing injuries involving multiple region of lower limb(s)
T062	Injuries of nerves involving multiple body regions
T063	Injuries of blood vessels involving multiple body regions
T068	Other specified injuries involving multiple body regions
T07X	Unspecified multiple injuries

5. Read codes to identify fracture due to neoplastic disease

Medcode	Read_code	Description
54834	N331700	Fracture of bone in neoplastic disease

6. ICD-10, OPCS and Read codes to identify infection

ICD-10 codes	Description	Deep/Superficial
A498	Other bacterial infections of unspecified site	Deep
A499	Bacterial infection, unspecified	Deep
A544	Gonococcal infection of musculoskeletal system	Deep
L088	Other spec local infections of skin and subcutaneous tissue	Superficial
L089	Local infection of skin and subcutaneous tissue, unspecified	Superficial
T814	Infection following a procedure, not elsewhere classified	Deep

Medcode	Read_code	Description	Deep/Superficial
3128	M07z.00	Local infection skin/subcut tissue NOS	Superficial
6956	SK03.00	Post-traumatic wound infection NEC	Deep
7155	N302.11	Bone infection	Deep
51854	SP25600	Postoperative wound infection-deep	Deep
20342	N30..00	Osteomyelitis, periostitis, other infections affecting bone	Deep
21073	M07y.00	Local infection of skin or subcutaneous tissue OS	Superficial
25363	SP06800	Infection and inflamm reac due inter ortho device	Deep
40293	SP06.00	Infection and inflammation due to internal prosthetic device	Deep
30381	SP05612	[X]Prosthetic infection	Deep
33381	A3Byz00	Other specified bacterial infection NOS	Superficial
43058	N30z.00	Bone infection NOS	Deep
39830	N300.12	Acute bone infection	Deep
40293	SP06.00	Infection and inflammation due to internal prosthetic device	Deep
52122	Myu0.00	[X]Infections of the skin and subcutaneous tissue	Superficial
69280	N30z600	Bone infection NOS, of the lower leg	Deep
69855	N30y600	Other infections involving bone, of the lower leg	Deep
4207	M03z000	Cellulitis NOS	Superficial

OPCS-4	Description	Deep/Superficial
S571	Debridement of skin NEC	Superficial
W332	Debridement of open fracture of bone	Deep
T963	Debridement of soft tissue NEC	Deep
W336	Debridement of bone NEC	Deep

7. OPCS-4 codes to identify procedures for debridement or introduction of therapeutic substance

OPCS-4	Description
S571	Debridement of skin NEC
W332	Debridement of open fracture of bone
T963	Debridement of soft tissue NEC

W336	Debridement of bone NEC
W283	Removal of internal fixation from bone NEC
X292	Continuous intravenous infusion of therapeutic substance NEC
S523	Insertion of therapeutic substance into subcutaneous tissue NEC
W351	Introduction of therapeutic substance into bone

8. OPCS-4 codes to identify procedures amputation of tibia bone

OPCS-4	Description
X094	Amputation of leg through knee
X095	Amputation of leg below knee
X098	Other specified amputation of leg
X099	Unspecified amputation of leg

9. Read codes to identify diabetes mellitus with and without complications

Medcodes	Read code	Description
231370	66AJ.11	Unstable diabetes
297735	C108600	Insulin dependent diabetes mellitus with gangrene
288454	C101100	Diabetes mellitus, adult onset, with ketoacidosis
344495	C10M.00	Lipoatrophic diabetes mellitus
224500	C103000	Diabetes mellitus, juvenile type, with ketoacidotic coma
233608	C109500	Non-insulin dependent diabetes mellitus with gangrene
251808	C109900	Non-insulin-dependent diabetes mellitus without complication
331810	C109412	Type 2 diabetes mellitus with ulcer
344028	C10FG00	Type 2 diabetes mellitus with arthropathy
279344	C109.11	NIDDM - Non-insulin dependent diabetes mellitus
343531	C109G11	Type II diabetes mellitus with arthropathy
279348	C10z.00	Diabetes mellitus with unspecified complication
342740	C10EM11	Type I diabetes mellitus with ketoacidosis
279343	C107200	Diabetes mellitus, adult with gangrene
210870	250 GA	Gangrene diabetic
339961	C10FJ00	Insulin treated Type 2 diabetes mellitus
308067	C108911	Type I diabetes mellitus maturity onset
297727	C102z00	Diabetes mellitus NOS with hyperosmolar coma
283820	250 HC	Hypoglycaemic Coma Diabetic
303253	250 AK	Maturity Onset Diabetes Mellitus Insulin
243302	G73y000	Diabetic Peripheral Angiopathy

Medcodes	Read code	Description
306131	250 E	Hypoglycaemia In Diabetes Mellitus
249566	66AJ.00	Diabetic - Poor Control
331925	C109J12	Insulin treated Type II diabetes mellitus
309010	C109F12	Type 2 diabetes mellitus with peripheral angiopathy
242649	C109300	Non-insulin-dependent diabetes mellitus with multiple comps
242646	C108400	Unstable insulin dependent diabetes mellitus
340367	C10F900	Type 2 diabetes mellitus without complication
206461	C10y.00	Diabetes mellitus with other specified manifestation
344412	C10F.11	Type II diabetes mellitus
341116	C10FL00	Type 2 diabetes mellitus with persistent proteinuria
306134	250 NT	UNSTABLE DIABETIC
309704	C109G00	Non-insulin dependent diabetes mellitus with arthropathy
343565	C109G12	Type 2 diabetes mellitus with arthropathy
249564	66A5.00	Diabetic on insulin
308094	C109511	Type II diabetes mellitus with gangrene
243795	L180600	Pre-existing diabetes mellitus, non-insulin-dependent
256384	250 PR	Pruritus Diabetic
341003	C10FN00	Type 2 diabetes mellitus with ketoacidosis
341356	C10E400	Unstable type 1 diabetes mellitus
270277	C10zy00	Other specified diabetes mellitus with unspecified comps
341680	C10D.00	Diabetes mellitus autosomal dominant type 2
288459	C107z00	Diabetes mellitus NOS with peripheral circulatory disorder
341002	C10EN00	Type 1 diabetes mellitus with ketoacidotic coma
303258	250 CT	Diabetic Cataract
215438	C101000	Diabetes mellitus, juvenile type, with ketoacidosis
206451	C100011	Insulin dependent diabetes mellitus
229069	250 JA	Diabetic Acidosis
309863	C108411	Unstable type I diabetes mellitus
303250	250 A	Sugar Diabetes
206452	C103.00	Diabetes mellitus with ketoacidotic coma
261004	C107.11	Diabetes mellitus with gangrene
303263	250 JL	Ketosis Diabetic
303256	250 AN	Diabetes
341598	C10E500	Type 1 diabetes mellitus with ulcer

Medcodes	Read code	Description
242650	C109400	Non-insulin dependent diabetes mellitus with ulcer
297739	C10yy00	Other specified diabetes mellitus with other spec comps
292948	250 AB	Abscess Diabetic
307957	C109711	Type II diabetes mellitus - poor control
261009	C10A000	Malnutrition-related diabetes mellitus with coma
339633	C10F.00	Type 2 diabetes mellitus
309658	C109J11	Insulin treated non-insulin dependent diabetes mellitus
223592	8A13.00	Diabetic stabilisation
233607	C108.00	Insulin dependent diabetes mellitus
347683	C10EG00	Type 1 diabetes mellitus with peripheral angiopathy
340865	C108E12	Type 1 diabetes mellitus with hypoglycaemic coma
302787	C108.13	Type I diabetes mellitus
270271	C107100	Diabetes mellitus, adult, peripheral circulatory disorder
233609	C10A100	Malnutrition-related diabetes mellitus with ketoacidosis
261001	C102000	Diabetes mellitus, juvenile type, with hyperosmolar coma
237987	250 AT	Diabetic Amyotrophy
308119	C109411	Type II diabetes mellitus with ulcer
341509	C10F500	Type 2 diabetes mellitus with gangrene
303262	250 JK	Ketoacidosis Diabetic
297726	C102100	Diabetes mellitus, adult onset, with hyperosmolar coma
308004	C108E11	Type I diabetes mellitus with hypoglycaemic coma
339527	C109K00	Hyperosmolar non-ketotic state in type 2 diabetes mellitus
247153	250 G	Ulcer Diabetic
258769	66AJz00	Diabetic - poor control NOS
347258	C10FJ11	Insulin treated Type II diabetes mellitus
297734	C108500	Insulin dependent diabetes mellitus with ulcer
309300	C109J00	Insulin treated Type 2 diabetes mellitus
341126	C10E800	Type 1 diabetes mellitus - poor control
309125	C108812	Type 1 diabetes mellitus - poor control
206454	C107400	NIDDM with peripheral circulatory disorder
343055	C10G.00	Secondary pancreatic diabetes mellitus
340580	C10EM00	Type 1 diabetes mellitus with ketoacidosis
331540	66AV.00	Diabetic on insulin and oral treatment
298869	L180500	Pre-existing diabetes mellitus, insulin-dependent

Medcodes	Read code	Description
342313	C10FP00	Type 2 diabetes mellitus with ketoacidotic coma
297725	C100.00	Diabetes mellitus with no mention of complication
344338	C10E600	Type 1 diabetes mellitus with gangrene
333576	C109D12	Type 2 diabetes mellitus with hypoglycaemic coma
341127	C10FF00	Type 2 diabetes mellitus with peripheral angiopathy
261005	C108.12	Type 1 diabetes mellitus
206457	C109.00	Non-insulin-dependent diabetes mellitus
331823	C109D00	Non-insulin dependent diabetes mellitus with hypoglyca coma
242656	C10zz00	Diabetes mellitus NOS with unspecified complication
340814	C10EE00	Type 1 diabetes mellitus with hypoglycaemic coma
295382	66AS.00	Diabetic annual review
233606	C107000	Diabetes mellitus, juvenile ??? circulatory disorder
347648	C10E412	Unstable insulin dependent diabetes mellitus
341139	C10E900	Type 1 diabetes mellitus maturity onset
242642	C101y00	Other specified diabetes mellitus with ketoacidosis
344989	C10FL11	Type II diabetes mellitus with persistent proteinuria
247152	250 DR	Diabetic Diarrhoea
283822	250 NH	Hyperosmolar Diabetic State
303259	250 DC	Dietary Control Diabetes
310005	C109712	Type 2 diabetes mellitus - poor control
270372	Cyu2.00	[X]Diabetes mellitus
270268	C10..00	Diabetes mellitus
346131	C10EA00	Type 1 diabetes mellitus without complication
279341	C100z00	Diabetes mellitus NOS with no mention of complication
297729	C103z00	Diabetes mellitus NOS with ketoacidotic coma
331809	C108G00	Insulin dependent diab mell with peripheral angiopathy
308089	C108E00	Insulin dependent diabetes mellitus with hypoglycaemic coma
215437	C101.00	Diabetes mellitus with ketoacidosis
347882	C10E812	Insulin dependent diabetes mellitus - poor control
341302	C10F700	Type 2 diabetes mellitus - poor control
222266	66AK.00	Diabetic - cooperative patient
270276	C10B000	Steroid induced diabetes mellitus without complication
233603	C100111	Maturity onset diabetes
339632	C10E.00	Type 1 diabetes mellitus

Medcodes	Read code	Description
223655	8H2J.00	Admit diabetic emergency
283823	2500AH	Latent Diabetes
285267	1434	H/O: diabetes mellitus
308820	C108811	Type I diabetes mellitus - poor control
344076	C10E.12	Insulin dependent diabetes mellitus
270269	C100100	Diabetes mellitus, adult onset, no mention of complication
341357	C10F400	Type 2 diabetes mellitus with ulcer
242655	C10z100	Diabetes mellitus, adult onset, unspecified complication
280482	L180X00	Pre-existing diabetes mellitus, unspecified
341557	8BL2.00	Patient on maximal tolerated therapy for diabetes
242653	C10yz00	Diabetes mellitus NOS with other specified manifestation
288455	C102.00	Diabetes mellitus with hyperosmolar coma
270275	C10A.00	Malnutrition-related diabetes mellitus
270273	C108.11	IDDM-Insulin dependent diabetes mellitus
215439	C101z00	Diabetes mellitus NOS with ketoacidosis
342317	C10FD00	Type 2 diabetes mellitus with hypoglycaemic coma
261007	C108800	Insulin dependent diabetes mellitus - poor control
303261	250 HP	Precoma Diabetic
341856	C10EK00	Type 1 diabetes mellitus with persistent proteinuria
303252	250 AD	Diabetes Mellitus Insulin Dependant
347025	C10H.00	Diabetes mellitus induced by non-steroid drugs
270270	C107.00	Diabetes mellitus with peripheral circulatory disorder
332066	C10D.11	Maturity onset diabetes in youth type 2
224506	C107300	IDDM with peripheral circulatory disorder
340332	C109F11	Type II diabetes mellitus with peripheral angiopathy
309143	C109D11	Type II diabetes mellitus with hypoglycaemic coma
341409	C10EL00	Type 1 diabetes mellitus with persistent microalbuminuria
242641	C100112	Non-insulin dependent diabetes mellitus
340474	C10FM00	Type 2 diabetes mellitus with persistent microalbuminuria
261095	Cyu2000	[X]Other specified diabetes mellitus
288460	C109.12	Type 2 diabetes mellitus
224501	C103y00	Other specified diabetes mellitus with coma
302788	C109.13	Type II diabetes mellitus
332948	C108511	Type I diabetes mellitus with ulcer

Medcodes	Read code	Description
347834	C10EN11	Type I diabetes mellitus with ketoacidotic coma
297738	C109700	Non-insulin dependent diabetes mellitus - poor control
283819	250 H	Coma Diabetic
215444	C10y100	Diabetes mellitus, adult, other specified manifestation
346130	C10E.11	Type I diabetes mellitus
344745	C10N.00	Secondary diabetes mellitus
347629	C10F711	Type II diabetes mellitus - poor control
277055	66AI.00	Diabetic - good control
251805	C100000	Diabetes mellitus, juvenile type, no mention of complication
206900	F464000	Diabetic cataract
309738	C109212	Type 2 diabetes mellitus with neurological complications
224502	C104000	Diabetes mellitus, juvenile type, with renal manifestation
345097	C109111	Type II diabetes mellitus with ophthalmic complications
341813	2BBP.00	O/E - right eye background diabetic retinopathy
346841	C108C11	Type I diabetes mellitus with polyneuropathy
308934	C108H00	Insulin dependent diabetes mellitus with arthropathy
215442	C109C00	Non-insulin dependent diabetes mellitus with nephropathy
261008	C108B00	Insulin dependent diabetes mellitus with mononeuropathy
297732	C106100	Diabetes mellitus, adult onset, neurological manifestation
206455	C108000	Insulin-dependent diabetes mellitus with renal complications
309524	C109H00	Non-insulin dependent d m with neuropathic arthropathy
251806	C108200	Insulin-dependent diabetes mellitus with neurological comps
343081	C10F100	Type 2 diabetes mellitus with ophthalmic complications
341814	2BBQ.00	O/E - left eye background diabetic retinopathy
309275	C109011	Type II diabetes mellitus with renal complications
252191	F420200	Preproliferative diabetic retinopathy
288456	C105000	Diabetes mellitus, juvenile type, ophthalmic manifestation
347472	C10FR00	Type 2 diabetes mellitus with gastroparesis
288461	C109100	Non-insulin-dependent diabetes mellitus with ophthalm comps
306132	250 F	Neuropathy Diabetic
341286	C10FE00	Type 2 diabetes mellitus with diabetic cataract
308948	C108712	Type 1 diabetes mellitus with retinopathy
242643	C106.13	Diabetes mellitus with polyneuropathy
279760	F420.00	Diabetic retinopathy

Medcodes	Read code	Description
308463	C109612	Type 2 diabetes mellitus with retinopathy
270274	C109B00	Non-insulin dependent diabetes mellitus with polyneuropathy
309943	F420600	Non proliferative diabetic retinopathy
288457	C105y00	Other specified diabetes mellitus with ophthalmic complicatn
309614	C109E11	Type II diabetes mellitus with diabetic cataract
341801	C10FB00	Type 2 diabetes mellitus with polyneuropathy
340973	C10FA00	Type 2 diabetes mellitus with mononeuropathy
347417	C10F611	Type II diabetes mellitus with retinopathy
343003	C10E200	Type 1 diabetes mellitus with neurological complications
342681	C108B11	Type I diabetes mellitus with mononeuropathy
206459	C109600	Non-insulin-dependent diabetes mellitus with retinopathy
298103	F381300	Myasthenic syndrome due to diabetic amyotrophy
224505	C106z00	Diabetes mellitus NOS with neurological manifestation
224503	C104y00	Other specified diabetes mellitus with renal complications
342469	2BBV.00	O/E - left eye proliferative diabetic retinopathy
332953	C108711	Type I diabetes mellitus with retinopathy
279761	F420400	Diabetic maculopathy
201928	250 LG	Diabetic Glomerulosclerosis
309628	C109C12	Type 2 diabetes mellitus with nephropathy
224504	C106.11	Diabetic amyotrophy
207385	K01x111	Kimmelstiel - Wilson disease
206456	C108D00	Insulin dependent diabetes mellitus with nephropathy
341836	C108212	Type 1 diabetes mellitus with neurological complications
242645	C108100	Insulin-dependent diabetes mellitus with ophthalmic comps
288858	F3y0.00	Diabetic mononeuropathy
252174	F372.12	Diabetic neuropathy
234015	F420300	Advanced diabetic maculopathy
347410	C10F011	Type II diabetes mellitus with renal complications
344952	2BBI.00	O/E - left eye stable treated prolif diabetic retinopathy
339960	C10FC00	Type 2 diabetes mellitus with nephropathy
343345	C10EF00	Type 1 diabetes mellitus with diabetic cataract
308504	C109E12	Type 2 diabetes mellitus with diabetic cataract
309757	C108D11	Type I diabetes mellitus with nephropathy
308851	C109B11	Type II diabetes mellitus with polyneuropathy

Medcodes	Read code	Description
341264	C10F200	Type 2 diabetes mellitus with neurological complications
346403	C10EB00	Type 1 diabetes mellitus with mononeuropathy
309007	C109H12	Type 2 diabetes mellitus with neuropathic arthropathy
333002	F420800	High risk non proliferative diabetic retinopathy
242647	C108700	Insulin dependent diabetes mellitus with retinopathy
341800	C10EC00	Type 1 diabetes mellitus with polyneuropathy
219965	250 M	Charcot's Diabetic Arthropathy
261411	F374z00	Polyneuropathy in disease NOS
309758	C109112	Type 2 diabetes mellitus with ophthalmic complications
306133	250 N	Diabetic Nephropathy
309796	2BBL.00	O/E - diabetic maculopathy present both eyes
331538	C109012	Type 2 diabetes mellitus with renal complications
242648	C109000	Non-insulin-dependent diabetes mellitus with renal comps
206458	C109200	Non-insulin-dependent diabetes mellitus with neuro comps
341701	F420700	High risk proliferative diabetic retinopathy
215440	C106.12	Diabetes mellitus with neuropathy
342045	2BBS.00	O/E - left eye preproliferative diabetic retinopathy
340163	C109E00	Non-insulin depend diabetes mellitus with diabetic cataract
340357	C10F600	Type 2 diabetes mellitus with retinopathy
297737	C108C00	Insulin dependent diabetes mellitus with polyneuropathy
336008	C108211	Type I diabetes mellitus with neurological complications
340987	C10E000	Type 1 diabetes mellitus with renal complications
310061	C109H11	Type II diabetes mellitus with neuropathic arthropathy
297731	C106.00	Diabetes mellitus with neurological manifestation
308830	C109611	Type II diabetes mellitus with retinopathy
233989	F372.11	Diabetic polyneuropathy
344951	2BBk.00	O/E - right eye stable treated prolif diabetic retinopathy
243072	F420z00	Diabetic retinopathy NOS
288458	C105z00	Diabetes mellitus NOS with ophthalmic manifestation
233604	C105100	Diabetes mellitus, adult onset, ophthalmic manifestation
340333	C10ED00	Type 1 diabetes mellitus with nephropathy
308871	C108F11	Type I diabetes mellitus with diabetic cataract
331568	C108011	Type I diabetes mellitus with renal complications
346291	C10FC11	Type II diabetes mellitus with nephropathy

Medcodes	Read code	Description
340162	C108012	Type 1 diabetes mellitus with renal complications
340507	C109A11	Type II diabetes mellitus with mononeuropathy
252180	F381311	Diabetic amyotrophy
308872	C109C11	Type II diabetes mellitus with nephropathy
347405	C10EQ00	Type 1 diabetes mellitus with gastroparesis
279345	C109A00	Non-insulin dependent diabetes mellitus with mononeuropathy
308715	C108F00	Insulin dependent diabetes mellitus with diabetic cataract
206453	C104.11	Diabetic nephropathy
342033	2BBR.00	O/E - right eye preproliferative diabetic retinopathy
333621	C108J12	Type 1 diabetes mellitus with neuropathic arthropathy
347771	C10FB11	Type II diabetes mellitus with polyneuropathy
297733	C106y00	Other specified diabetes mellitus with neurological comps
256383	250 LK	Kimmelstiel- Wilson Disease/Syndrome
340257	C10FH00	Type 2 diabetes mellitus with neuropathic arthropathy
341459	C10F000	Type 2 diabetes mellitus with renal complications
297730	C105.00	Diabetes mellitus with ophthalmic manifestation
261428	F420100	Proliferative diabetic retinopathy
333249	C109211	Type II diabetes mellitus with neurological complications
261003	C104z00	Diabetes mellitis with nephropathy NOS
341221	C10E100	Type 1 diabetes mellitus with ophthalmic complications

10. Read codes to identify dyspnoea

Medcode	Read_code	Description
3092	R060A00	[D]Dyspnoea
6434	1736.00	Paroxysmal nocturnal dyspnoea
7000	2322.00	O/E - dyspnoea
18116	173D.00	Nocturnal dyspnoea
53771	173C.11	Dyspnoea on exertion

11. Read codes to identify ventilator requirement

Medcode	Read_code	Description
87337	7M36300	Ventilatory support

12. Read codes to identify COPD

Medcode	Read code	Description
1001	H3...00	Chronic obstructive pulmonary disease
9520	66YB.00	Chronic obstructive pulmonary disease monitoring
9876	H38..00	Severe chronic obstructive pulmonary disease
10802	H37..00	Moderate chronic obstructive pulmonary disease
10863	H36..00	Mild chronic obstructive pulmonary disease
11287	66YM.00	Chronic obstructive pulmonary disease annual review
18621	66YL.00	Chronic obstructive pulmonary disease follow-up
37247	H3z..11	Chronic obstructive pulmonary disease NOS
45770	66Yg.00	Chronic obstructive pulmonary disease disturbs sleep
45771	66Yh.00	Chronic obstructive pulmonary disease does not disturb sleep
65733	Hyu3100	[X]Other specified chronic obstructive pulmonary disease
67040	H3y..11	Other specified chronic obstructive pulmonary disease
93568	H39..00	Very severe chronic obstructive pulmonary disease
102685	66YB000	Chronic obstructive pulmonary disease 3 monthly review
103007	66YB100	Chronic obstructive pulmonary disease 6 monthly review
103494	14B3.12	History of chronic obstructive pulmonary disease
104985	9NgP.00	On chronic obstructive pulmonary disease supprtv cre pathway
105457	8CMW500	Chronic obstructive pulmonary disease care pathway

13. Read codes to identify heart failure

Medcode	Read_code	Description
398	G580.00	Congestive heart failure
2062	G58..00	Heart failure
4024	G58z.00	Heart failure NOS
9913	1O1..00	Heart failure confirmed
10079	G580.12	Right heart failure
15058	14A6.00	H/O: heart failure
17851	8HBE.00	Heart failure follow-up
21837	G232.00	Hypertensive heart&renal dis wth (congestive) heart failure
23707	G580000	Acute congestive heart failure
27964	G582.00	Acute heart failure
28684	G233.00	Hypertensive heart and renal disease with renal failure
30779	662W.00	Heart failure annual review
32671	G580100	Chronic congestive heart failure

Medcode	Read_code	Description
32898	8H2S.00	Admit heart failure emergency
32911	9Or..00	Heart failure monitoring administration
32945	8CL3.00	Heart failure care plan discussed with patient
46912	14AM.00	H/O: Heart failure in last year
60099	67D4.00	Heart failure information given to patient
66306	SP11111	Heart failure as a complication of care
69062	9N6T.00	Referred by heart failure nurse specialist
71235	8Hk0.00	Referred to heart failure education group
83502	662p.00	Heart failure 6 month review
94870	G580400	Congestive heart failure due to valvular disease
96799	G5y4z00	Post cardiac operation heart failure NOS
101137	G583.11	HFNEF - heart failure with normal ejection fraction
101138	G583.00	Heart failure with normal ejection fraction
103732	8CMK.00	Has heart failure management plan
105002	679W100	Education about deteriorating heart failure
105542	8CeC.00	Preferred place of care for next exacerbation heart failure
106198	661M500	Heart failure self-management plan agreed

14. Read codes to identify renal failure

Medcode	Read_code	Description
350	K06..00	Renal failure unspecified
512	K05..00	Chronic renal failure
2266	K04..00	Acute renal failure
6712	K050.00	End stage renal failure
11554	SP15400	Renal failure as a complication of care
11773	7L1A.11	Dialysis for renal failure
15945	SK05.00	Renal failure following crush syndrome
16929	D215.00	Anaemia secondary to renal failure
24292	SP15412	Post operative renal failure
24676	SK08.00	Acute renal failure due to rhabdomyolysis
25394	D215000	Anaemia secondary to chronic renal failure
25582	K04z.00	Acute renal failure NOS
28684	G233.00	Hypertensive heart and renal disease with renal failure
31549	7L1A.00	Compensation for renal failure
32423	G222.00	Hypertensive renal disease with renal failure

Medcode	Read_code	Description
35235	K04y.00	Other acute renal failure
48022	7L1Ay00	Other specified compensation for renal failure
53852	K05..12	End stage renal failure
53940	Kyu2100	[X]Other chronic renal failure
53945	Kyu2000	[X]Other acute renal failure
56760	7L1B.00	Placement ambulatory apparatus compensation renal failure
57919	K043.00	Acute drug-induced renal failure
59194	7L1By00	Placement ambulatory apparatus- compensate renal failure OS
61930	Kyu2.00	[X]Renal failure
63277	L393.00	Acute renal failure following labour and delivery
63760	SK05.11	Renal failure after crushing
64636	7L1Az00	Compensation for renal failure NOS
65089	7L1Cz00	Placement other apparatus- compensate for renal failure NOS
71314	L093.00	Renal failure following abortive pregnancy
72458	L393000	Post-delivery acute renal failure unspecified
83513	7L1C.00	Placement other apparatus for compensation for renal failure
96179	L393100	Post-delivery acute renal failure - delivered with p/n prob
97198	K044.00	Acute renal failure due to urinary obstruction
100205	K0E..00	Acute-on-chronic renal failure
101666	L070300	Unspecified abortion with renal failure
104857	K043000	Acute renal failure due to ACE inhibitor
105209	K045.00	Acute renal failure due to non-traumatic rhabdomyolysis
105267	K04B.00	Acute renal failure due to traumatic rhabdomyolysis
105739	K04..11	ARF - Acute renal failure
106860	C353600	Renal failure-associated hyperphosphataemia
107241	K043400	Acute renal failure induced by non-steroid anti-inflamm drug

15. Read codes to identify hypertension

Medcode	Read_code	Description
799	G20..00	Essential hypertension
1894	G201.00	Benign essential hypertension
2666	14A2.00	H/O: hypertension
3425	662O.00	On treatment for hypertension
3712	G20z.11	Hypertension NOS
4372	G202.00	Systolic hypertension

Medcode	Read_code	Description
7329	G24..00	Secondary hypertension
10818	G20z.00	Essential hypertension NOS
12680	8CR4.00	Hypertension clinical management plan
15377	G200.00	Malignant essential hypertension
16059	G24z.00	Secondary hypertension NOS
16565	6627	Good hypertension control
18482	662c.00	Hypertension six month review
18590	662b.00	Moderate hypertension control
19070	662d.00	Hypertension annual review
21826	662F.00	Hypertension treatm. started
25371	G241000	Secondary benign renovascular hypertension
27511	6628	Poor hypertension control
30776	6629	Hypertension:follow-up default
31387	G24z000	Secondary renovascular hypertension NOS
31755	G240.00	Secondary malignant hypertension
34744	G244.00	Hypertension secondary to endocrine disorders
42229	G24zz00	Secondary hypertension NOS
44549	L128.00	Pre-exist hypertension compl preg childbirth and puerperium
51635	G241z00	Secondary benign hypertension NOS
57288	G241.00	Secondary benign hypertension
59383	G240000	Secondary malignant renovascular hypertension
73293	G240z00	Secondary malignant hypertension NOS
83473	G203.00	Diastolic hypertension
85944	7Q01.00	High cost hypertension drugs
97533	Gyu2100	[X]Hypertension secondary to other renal disorders
98230	67H8.00	Lifestyle advice regarding hypertension
101649	7Q01y00	Other specified high cost hypertension drugs
102406	662P000	Hypertension 9 month review
102458	Gyu2000	[X]Other secondary hypertension
105274	G28..00	Stage 2 hypertension (NICE - Nat Ins for Hth Clin Excl 2011)
105316	G25..11	Stage 1 hypertension
105371	G25..00	Stage 1 hypertension (NICE - Nat Ins for Hth Clin Excl 2011)
105480	G27..00	Hypertension resistant to drug therapy
105487	G26..11	Severe hypertension

Medcode	Read_code	Description
105989	G26..00	Severe hypertension (Nat Inst for Health Clinical Ex 2011)
61166	G21z000	Hypertensive heart disease NOS without CCF
61660	G211000	Benign hypertensive heart disease without CCF
95334	G210000	Malignant hypertensive heart disease without CCF

16. Codes to identify open and closed tibial shaft fracture

Medcode	Read_code	Description
20678	S333200	Open fracture of tibia and fibula, shaft
28068	S333.00	Open fracture of tibia/fibula, shaft
28118	S333000	Open fracture shaft of tibia
28198	S333z00	Open fracture of tibia and fibula, shaft, NOS
28233	S33y.00	Open fracture of tibia and fibula, unspecified part, NOS
29084	S33y200	Open fracture of tibia and fibula, unspecified part
29164	S33y000	Open fracture of tibia, unspecified part, NOS

Medcode	Read_code	Description
971	S33x000	Closed fracture of tibia, unspecified part, NOS
4572	S33x200	Closed fracture of tibia and fibula, unspecified part
29109	S33x.00	Closed fracture of tibia and fibula, unspecified part, NOS
29121	S332.00	Closed fracture of tibia/fibula, shaft
33520	S332200	Closed fracture of tibia and fibula, shaft
34021	S332000	Closed fracture shaft of tibia
41971	S33xz00	Closed fracture of tibia and fibula, unspecified part, NOS
55464	S332z00	Closed fracture of tibia and fibula, shaft, NOS

OPCS-4	Description	Open/closed fracture
S571	Debridement of skin NEC	Open
W332	Debridement of open fracture of bone	Open
T963	Debridement of soft tissue NEC	Open
W336	Debridement of bone NEC	Open

ICD-10	Description	Open/closed fracture
T14.1	Open wound of unspecified body region	Open
T01.3	Open wounds involving multiple regions of lower limb(s)	Open
S81.7	Multiple open wounds of lower leg	Open

ICD-10	Description	Open/closed fracture
S81.8	Open wound of other parts of lower leg	Open
S81.9	Open wound of lower leg, part unspecified	Open
T93.0	Sequelae of open wound of lower limb	Open
T93.2	Sequelae of other fractures of lower limb	Open
T01.9	Multiple open wounds, unspecified	Open
T13.1	Open wound of lower limb, level unspecified	Open
T01.8	Open wounds involving other combinations of body regions	Open
T94.0	Sequelae of injuries involving multiple body regions	Open
T94.1	Sequelae of injuries, not specified by body region	Open
T12.1	Fracture of lower limb, level unspecified, open	Open

17. Read codes to identify Charlson comorbidity index

Microsoft Excel 2003 Worksheet

18. OPCS Codes to identify reoperations

OPCS-4	Description
W242	Closed reduction of fracture of long bone and rigid internal fixation NEC
O172	Remanipulation of fracture of long bone and rigid internal fixation NEC
O173	Remanipulation of fracture of long bone and flexible internal fixation HFQ
O175	Remanipulation of fragment of bone and fixation using screw
O178	Other specified secondary closed reduction of fracture of bone and internal fixation
O179	Unspecified secondary closed reduction of fracture of bone and internal fixation
W231	Secondary open reduction of fracture of bone and intramedullary fixation HFQ
W232	Secondary open reduction of fracture of bone and extramedullary fixation HFQ
W236	Secondary open reduction of fracture of bone and internal fixation HFQ
W248	Other specified closed reduction of fracture of bone and internal fixation
W249	Unspecified closed reduction of fracture of bone and internal fixation
W281	Application of internal fixation to bone NEC
W282	Adjustment to internal fixation of bone NEC
W283	Removal of internal fixation from bone NEC
W288	Other specified other internal fixation of bone
W289	Unspecified other internal fixation of bone

OPCS-4	Description
W235	Secondary open reduction of fracture of bone and external fixation HFQ
W252	Closed reduction of fracture of bone and fixation using functional bracing system
W253	Remanipulation of fracture of bone and external fixation HFQ
W258	Other specified closed reduction of fracture of bone and external fixation
W259	Unspecified closed reduction of fracture of bone and external fixation
W301	Application of external fixation to bone NEC
W302	Adjustment to external fixation of bone NEC
W303	Removal of external fixation from bone NEC
W304	Application of external ring fixation to bone NEC
W308	Other specified other external fixation of bone
W309	Unspecified other external fixation of bone
W35.3	Removal of implanted substance from bone
W32	Other graft of bone
W32.1	Prepared graft of bone
W32.2	Allograft of bone NEC
W32.3	Xenograft of bone
W32.4	Synthetic graft of bone
W32.5	Cancellous chip allograft of bone
W32.8	Other specified other graft of bone
W32.9	Unspecified other graft of bone
S31.3	Revision of flap of skin NEC

Additional file 2: Baseline and results at all time points

Table C1. Patient demographic and clinical characteristics at all time points

	All enrolled patients (N=805)	Index stay			30 days			90 days			1 year			2 years		
		No infection (N=775)	Infection (N=30)	p-value[a]	No infection (N=736)	Infection (N=64)	p-value[a]	No infection (N=699)	Infection (N=71)	p-value[a]	No infection (N=606)	Infection (N=80)	p-value[a]	No infection (N=509)	Infection (N=79)	p-value[a]
Demographics																
Age (years), mean (SD)	40.8 (17.2)	40.7 (16.8)	43.0 (23.9)	0.61	40.5 (16.9)	44.0 (19.1)	0.17	40.7 (16.9)	43.8 (19.1)	0.20	40.7 (16.8)	45.1 (19.1)	0.06	40.5 (16.4)	46.4 (20.0)	0.02
Gender, n (%)				0.84			1.00			1.00			0.89			1.00
Male	590 (73.3)	569 (73.4)	21 (70.0)		539 (73.2)	47 (73.4)		508 (72.7)	52 (73.2)		438 (72.3)	59 (73.8)		368 (72.3)	57 (72.2)	
Clinical history/comorbidities																
Charlson score, mean (SD)	0.04 (0.23)	0.04 (0.24)	0.00 (0.00)	<0.001	0.04 (0.24)	0.02 (0.12)	0.22	0.04 (0.3)	0.01 (0.12)	0.13	0.04 (0.24)	0.01 (0.11)	0.11	0.03 (0.22)	0.01 (0.11)	0.25
Smoker, n (%)	256 (31.8)	247 (31.9)	9 (30.0)	0.99	239 (32.5)	17 (26.6)	0.41	233 (33.3)	18 (25.4)	0.22	202 (33.3)	20 (25.0)	0.17	160 (31.4)	19 (24.1)	0.23
Diabetes, n (%)	27 (3.4)	27 (3.5)	0 (0.0)	0.62	26 (3.5)	1 (1.6)	0.72	26 (3.7)	1 (1.4)	0.50	21 (3.5)	3 (3.8)	0.75	15 (3.0)	3 (3.8)	0.72
COPD, n (%)	8 (1.0)	8 (1.0)	0 (0.0)	1.00	8 (1.1)	0 (0.0)	1.00	7 (1.0)	0 (0.0)	1.00	6 (1.0)	1 (1.3)	0.58	3 (0.6)	1 (1.3)	0.44
Congestive heart failure, n (%)	2 (0.3)	2 (0.3)	0 (0.0)	1.00	2 (0.3)	0 (0.0)	1.00	1 (0.1)	0 (0.0)	1.00	0 (0.0)	0 (0.0)	NA	0 (0.0)	0 (0.0)	NA
Hypertension, n (%)	12 (1.5)	12 (1.6)	0 (0.0)	1.00	12 (1.6)	0 (0.0)	0.61	12 (1.7)	0 (0.0)	0.62	10 (1.7)	0 (0.0)	0.62	7 (1.4)	0 (0.0)	0.60
Compartment syndrome, n (%)	27 (3.4)	22 (2.8)	5 (16.7)	0.00	19 (2.6)	8 (12.5)	<0.05	18 (2.6)	8 (11.3)	<0.05	17 (2.8)	9 (11.2)	0.00	15 (3.0)	8 (10.1)	<0.05
Index episode																
Year of intramedullary nailing, mean (SD)	2009 (3.6)	2009 (3.6)	2009 (3.6)	0.72	2009 (3.6)	2009 (3.6)	0.99	2009 (3.6)	2009 (3.6)	0.74	2008 (3.4)	2008 (3.4)	0.99	2008 (3.1)	2008 (3.1)	0.85
Inpatient waiting time (days) for surgery, mean (SD)	1.4 (2.4)	1.4 (2.4)	0.7 (2.4)	0.14	1.4 (2.4)	0.7 (1.7)	<0.05	1.4 (2.5)	0.8 (1.7)	<0.05	1.4 (2.4)	0.6 (1.0)	<0.001	1.4 (2.2)	0.6 (1.0)	<0.001
Fracture type, n (%)				<0.001			<0.001			<0.001			<0.001			<0.001
Closed fracture	663 (82.4)	648 (83.6)	15 (50.0)		624 (84.8)	35 (54.7)		595 (85.1)	42 (59.2)		524 (86.5)	49 (61.3)		438 (86.1)	52 (65.8)	

	All enrolled patients (N=805)	Index stay			30 days			90 days			1 year			2 years		
		No infection (N=775)	Infection (N=30)	p-value[a]	No infection (N=736)	Infection (N=64)	p-value[a]	No infection (N=699)	Infection (N=71)	p-value[a]	No infection (N=606)	Infection (N=80)	p-value[a]	No infection (N=509)	Infection (N=79)	p-value[a]
Received ≥1 prescription for antibiotics in the 12 months prior to the index stay, n (%)	60 (7.5)	60 (7.7)	0 (0.0)	0.16	57 (7.7)	3 (4.7)	0.47	56 (8.0)	3 (4.2)	0.36	47 (7.8)	4 (5.0)	0.51	35 (6.9)	5 (6.3)	1.000
Received ≥1 prescription for opioids in the 12 months prior to the index stay, n (%)	16 (2.0)	15 (1.9)	1 (3.3)	0.46	15 (2.0)	1 (1.6)	1.00	15 (2.2)	1 (1.4)	1.00	11 (1.8)	2 (2.5)	0.66	8 (1.6)	2 (2.5)	0.63

Abbreviations: COPD, chronic obstructive pulmonary disease; NA, not applicable; SD, standard deviation.

[a] No infection versus infection, t-tests were performed for comparison of continuous variables and chi-squared (or Fisher exact tests when n was <5) for comparison of categorical variables.

Table D1. Comparative results at all time points

Time period	Endpoint	Bivariate analysis, mean (SD)		Multivariate analysis, mean (95% CI)		Absolute difference (multivariate analysis)
		Infection	No infection	Infection	No infection	
Index stay *(N infection = 30; N no infection = 775)*	Total costs (£)	11,695 (6,553)	6,669 (3,133; p<0.001)	10,384 (8,900, 12,116)	6,603 (6,411, 6,802)	3,781 p<0.001
	Inpatient costs (£)	11,695 (6,553)	6,669 (3,133; p<0.001)	10,384 (8,900, 12,116)	6,603 (6,411, 6,802)	3,781 p<0.001
	LOS (days)	22.6 (20.0)	9.7 (12.1; p<0.001)	17.6 (13.0, 23.7)	8.5 (8.0, 9.0)	9.05 p<0.001
	ICU LOS (days)	1.5 (8.2)	0.1 (1.1; p=0.53)	0.1 (0.1, 0.2)	0.0 (0.0, 0.01)	0.115 p<0.001
	Reoperations (number)	0.3 (0.8)	0.0 (0.1; p<0.001)	0.1 (0.0, 0.2)	0.0 (0.0, 0.0)	0.070 p<0.001
	Reoperations (rate, %)	13.3	1.3 (p<0.001)	9.7 (3.1, 26.3)	1.1 (0.5, 2.1)	8.6 p<0.001

Time period	Endpoint	Bivariate analysis, mean (SD)		Multivariate analysis, mean (95% CI)		Absolute difference (multivariate analysis)
		Infection	No infection	Infection	No infection	
Index stay + 30 days post-discharge *(N infection = 64; N no infection = 736)*	Total costs (£)	12,673 (7,345)	7,089 (3,588; p<0.001)	11,257 (10,045, 12,615)	7,017 (6,792, 7,248)	4,241 p<0.001
	Inpatient costs (£)	12,367 (7,290)	6,829 (3,397; p<0.001)	11,008 (9,818, 12,343)	6,768 (6,551, 6,993)	4,240 p<0.001
	Hospital outpatient/ambulatory costs (£)	215 (116)	155 (94; p=0.4)	245 (145, 345)	152 (125, 179)	93 p=0.07
	Primary care costs (£)	289 (555)	254 (673, p=0.24)	243 (139, 426)	205 (175, 241)	38 p=0.57
	LOS (days)	19.3 (19.2)	10.1 (12.2; p<0.001)	15.0 (12.1, 18.6)	8.9 (8.4, 9.5)	6.1 p<0.001
	ICU LOS (days)	0.7 (5.6)	0.1 (1.1; p=0.4)	0.1 (0.0, 0.1)	0.0 (0.0, 0.0)	0.0 p<0.001
	Readmissions (number)	0.6 (0.6)	0.1 (0.3; p<0.001)	0.5 (0.4, 0.7)	0.1 (0.1, 0.1)	0.4 p<0.001
	Readmissions (rate, %)	48.4	7.6 (p<0.001)	44.1 (31.5, 57.5)	7.1 (5.4, 9.2)	37.0 p<0.001
	Reoperations (number)	0.2 (0.7)	0.0 (0.1; p<0.001)	0.1 (0.1, 0.2)	0.0 (0.0, 0.0)	0.1 p<0.001
	Reoperations (rate, %)	14.1	1.6 (p<0.001)	11.5 (5.4, 22.9)	1.3 (0.7, 2.5)	10.2 p<0.001
	Amputation (rate, %)	3.1	0.1 (p<0.01)	Not feasible		
	Hospital outpatient/ambulatory referrals (number)	1.6 (0.9)	1.2 (0.5; p=0.28)	1.6 (1.1, 2.2)	1.21 (1.0, 1.4)	0.45 p=0.13
	Total costs (£)	13,621 (7,827)	7,527 (4,326; p<0.001)	11,949 (10,634,13,427)	7,423 (7,160, 7,696)	4,526 p<0.001
	Inpatient costs (£)	13,154 (7,673)	7,157 (4,111; p<0.001)	11,532 (10,246,12,979)	7,072 (6,818, 7,336)	4,459 p<0.001

Time period	Endpoint	Bivariate analysis, mean (SD)		Multivariate analysis, mean (95% CI)		Absolute difference (multivariate analysis)
		Infection	No infection	Infection	No infection	
Index stay + 90 days post-discharge *(N infection = 71; N no infection = 699)*	Hospital outpatient/ambulatory costs (£)	183 (87)	171 (135; p=0.53)	194 (125, 264)	170 (141, 198)	25 p=0.515
	Primary care costs (£)	436 (637)	353 (737; p<0.05)	428 (290, 630)	299 (264, 338)	129 p=0.084
	LOS (days)	21.7 (21.5)	11.1 (14.6 p<0.001)	16.4 (13.2, 20.4)	9.6 (9.0, 10.3)	6.8 p<0.001
	ICU LOS (days)	0.7 (5.3)	0.1 (1.2; p=0.576)	0.0 (0.0, 0.1)	0.0 (0.0, 0.0)	0.0 p<0.001
	Readmissions (number)	0.8 (0.8)	0.2 (0.6; p<0.001)	0.7 (0.5, 0.9)	0.2 (0.2, 0.2)	0.5 p<0.001
	Readmissions (rate, %)	57.7	17.2 (p<0.001)	5.4 (41.5, 65.9)	16.5 (13.9, 19.5)	37.4 p<0.001
	Reoperations (number)	0.3 (0.7)	0.1 (0.3; p<0.001)	0.2 (0.1, 0.3)	0.1 (0.0, 0.1)	0.1 p=0.001
	Reoperations (rate, %)	18.3	6.0 (p<0.001)	14.3 (7.7, 25.0)	5.4 (3.9, 7.4)	9.0 p<0.05
	Amputation (rate, %)	2.8	0.1 (p<0.05)	Not feasible		
	Hospital outpatient/ambulatory referrals (number)	1.2 (0.6)	1.4 (0.9; p=0.92)	1.3 (0.9, 1.7)	1.4 (1.2, 1.5)	0.0 p=0.835
Index stay + 1 year post-discharge *(N infection = 80; N no infection = 606)*	Total costs (£)	16,800 (12,663)	8,435 (5,330; p<0.001)	14,756 (13,123, 16,593)	8,279 (7,946, 8,626)	6,478 p<0.001
	Inpatient costs (£)	15,580 (11,872)	7,746 (5,060; p<0.001)	13,672 (12,122, 15,420)	7,616 (7,301, 7,944)	6,056 p<0.001
	Hospital outpatient/ambulatory costs (£)	250 (251)	239 (218; p=0.77)	220 (151, 288)	244 (211, 277)	25 p=0.516
	Primary care costs (£)	1,139 (1,657)	630 (903; p<0.001)	1,017 (769, 1,344)	551 (498, 609)	466 p<0.001

Time period	Endpoint	Bivariate analysis, mean (SD)		Multivariate analysis, mean (95% CI)		Absolute difference (multivariate analysis)
		Infection	No infection	Infection	No infection	
	LOS (days)	28.5 (33.3)	12.6 (21.3; p<0.001)	21.9 (17.3, 27.7)	10.5 (9.7, 11.4)	11.4 p<0.001
	ICU LOS (days)	0.2 (1.5)	0.1 (1.1; p=0.758)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 p=0.914
	Readmissions (number)	1.5 (1.5)	0.5 (0.9; p<0.001)	1.5 (1.2, 1.8)	0.5 (0.4, 0.6)	1.0 p<0.001
	Readmissions (rate, %)	75	36 (p<0.001)	74.4 (63.4, 83.0)	35.9 (32.1, 39.9)	38.5 p<0.001
	Reoperations (number)	0.6 (1.0)	0.2 (0.5; p<0.001)	0.6 (0.5, 0.8)	0.2 (0.2, 0.3)	0.4 p<0.001
	Reoperations (rate, %)	37.5	21.3 (p<0.01)	38.6 (28.3, 50.0)	20.3 (17.2, 23.8)	18.2 p<0.001
	Amputation (rate, %)	2.5	0.2 (p<0.05)	Not feasible		
	Hospital outpatient/ambulatory referrals (number)	1.8 (1.6)	1.8 (1.5; p=0.66)	1.7 (1.2, 2.1)	1.8 (1.6, 2.1)	0.2 p=0.44
Index stay + 2 years post-discharge *(N infection = 79; N no infection = 509)*	Total costs (£)	18,779 (14,929)	9,611 (6,284; p<0.001)	16,626 (14,664, 18,849)	9,439 (8,998, 9,901)	7,187 p<0.001
	Inpatient costs (£)	16,900 (13,720)	8,573 (5,729; p<0.001)	14,898 (13,106, 16,935)	8,447 (8,044, 8,871)	6,451 p<0.001
	Hospital outpatient/ambulatory costs (£)	282 (296)	275 (265; p=0.893)	264 (189, 338)	277 (243, 310)	13 p=0.747
	Primary care costs (£)	1,758 (2,437)	929 (1,179; p<0.01)	1,487 (1,149, 1,924)	821 (742, 907)	666 p<0.001
	LOS (days)	31.5 (38.1)	13.4 (22.6; p<0.001)	24.6 (19.6, 30.8)	11.3 (10.4, 12.3)	13.3 p<0.001
	ICU LOS (days)	0.2 (1.5)	0.1 (1.2; p=0.24)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 p=0.20

Time period	Endpoint	Bivariate analysis, mean (SD)		Multivariate analysis, mean (95% CI)		Absolute difference (multivariate analysis)
		Infection	No infection	Infection	No infection	
	Readmissions (number)	2.1 (2.3)	1.0 (1.5; p<0.001)	2.2 (1.9, 2.6)	0.9 (0.8, 1.0)	1.3 p<0.001
	Readmissions (rate, %)	77.2	51.1 (p<0.001)	77.6 (67.0, 85.6)	51.4 (46.9, 56.8)	26.3 p<0.001
	Reoperations (number)	0.8 (1.1)	0.4 (0.7; p<0.01)	0.8 (0.6, 1.0)	0.4 (0.3, 0.4)	0.4 p<0.001
	Reoperations (rate, %)	46.8	32.4 (p<0.05)	49.0 (37.7, 60.3)	31.2 (27.2, 35.5)	17.7 p<0.05
	Amputation (rate, %)	3.8	0.2 (p<0.01)	Not feasible		
	Hospital outpatient/ambulatory referrals (number)	2.0 (2.0)	2.1 (1.9; p=0.55)	2.0 (1.5, 2.5)	2.1 (1.8, 2.3)	0.1 p=0.82

Abbreviations: CI, confidence interval; ICU, intensive care unit; LOS, length of stay; NA, not applicable; SD, standard deviation.

Table D2. 1 year cost breakdown (£) – inpatient setting

Endpoint	Bivariate analysis, mean (SD)	
	Infection	No infection
Total inpatient costs	15,580 (11,872)	7,746 (5,060)
HRG costs	15,488 (11,743)	7,702 (4,985)
Unbundled HRG costs	36 (116)	16 (72)
Critical care costs	56 (381)	26 (208)
Specialised care costs	0 (0)	2 (42)

Abbreviations: HRG, Healthcare Resource Group; SD, standard deviation.

Table D3. 1 year healthcare resource use and cost breakdown – primary care

Endpoint	Bivariate analysis, mean (SD)	
	Infection	No infection
Costs (£)		
Total primary care costs	1,139 (1,657)	630 (903)
Total drug costs	368 (1,031)	198 (681)
Total test costs	147 (247)	95 (186)
Imaging test costs	27 (71)	25 (72)
Total consultation costs	625 (721)	338 (334)
GP	322 (317)	212 (225)
Nurse	140 (362)	36 (75)
Other healthcare professional	120 (243)	55 (121)
Administrative	42 (36)	35 (30)
Healthcare resource use (number)		
Total tests	25 (52)	14 (30)
Imaging tests	0.4 (0.8)	0.5 (1.5)
Total consultations	52 (51)	33 (25)
GP	14 (13)	9 (9)
Nurse	10 (21)	3 (5)
Other healthcare professional	9 (17)	4 (8)
Administrative	22 (18)	18 (15)

Abbreviations: GP, General Practitioner; SD, standard deviation.

Table D4. Subgroup analyses of 1 year inpatient costs – infection type (deep versus superficial)

	No infection (N=606)	Superficial infection (N=54)	Deep infection (N=26)
Bivariate analysis, mean (SD)	£7,746 (£5,060)	£14,232 (£8,633)	£18,378 (£16,592)
Multivariate analysis, mean (95% CI)[a]	£7,614 (£7,301, £7,941)	£12,814 (£11,093, £14,803)	£15,513 (£12,640, £19,040)

Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; SD, standard deviation.

[a] Adjusted for open/closed fracture, age, smoker, year at index, diabetes, COPD, days prior nailing and compartment syndrome.

Table D5. Subgroup analyses of 1 year inpatient costs – fracture type (open versus closed)

	No infection (N=606)		Infection (N=80)	
Fracture type	**Closed (N=524)**	**Open (N=82)**	**Closed (N=49)**	**Open (N=31)**
Bivariate analysis, mean (SD)	£7,433 (£3,957)	£9,741 (£9,247)	£12,291 (£7,366)	£20,778 (£15,451)
Multivariate analysis, mean (95% CI)[a]	£7,278 (£6,956, £7,614)	£9,495 (£8,469, £10,645)	£12,178 (£10,492, £14,136)	£19,542 (£16,166, £23,623)

Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; SD, standard deviation.

[a] Adjusted for age, smoker, year at index, diabetes, COPD, days prior nailing and compartment syndrome.

Table D6. Sensitivity analyses

Time period	Endpoint	Bivariate analysis, mean (SD)		Multivariate analysis, mean (95% CI)		Absolute difference (multivariate analysis)
		Infection	No infection	Infection	No infection	
Index stay *(N infection = 24; N no infection = 564)*	Total costs (£)	12,554 (6,832)	6,580 (3,123; p<0.001)	11,110 (9,328, 13,232)	6,517 (6,295, 6,747)	4,593 p<0.001
	LOS (days)	24.2 (20.9)	9.4 (11.7; p<0.001)	18.6 (13.1, 26.4)	8.5 (7.9, 9.1)	10.1 p<0.001
	Reoperations (number)	0.3 (0.9)	0.0 (0.1; p<0.001)	0.1 (0.0, 0.3)	0.0 (0.0, 0.0)	0.1 p<0.001
	Reoperations (rate)	12.5	1.6 (p<0.01)	9.9 (2.7, 30.6)	1.4 (0.7, 2.8)	8.5 p<0.05
Index stay + 30 days post-discharge *(N infection = 51; N no infection = 537)*	Total costs (£)	12,957 (7,385)	7,077 (3,747; p<0.001)	11,453 (10,016, 13,096)	7,010 (6,739, 7,292)	4,444 p<0.001
	LOS (days)	20.2 (19.4)	10.0 (12.4; p<0.001)	15.6 (12.1, 20.0)	9.1 (8.4, 9.8)	6.5 p<0.001
	Readmissions (number)	0.6 (0.6)	0.1 (0.3; p<0.001)	0.5 (0.3, 0.7)	0.1 (0.1, 0.1)	0.4 p<0.001
	Readmissions (rate)	47.1	8.4 (p<0.001)	45.7 (32.0, 60.0)	7.9 (5.9, 10.5)	37.8 p<0.001
	Reoperations (number)	0.3 (0.7)	0.0 (0.2; p<0.001)	0.1 (0.1, 0.3)	0.0 (0.0, 0.0)	0.1 p<0.001
	Reoperations (rate)	13.7	2.2 (p<0.001)	11.7 (5.0, 25.3)	1.8 (1.0, 3.4)	9.9 p<0.001
Index stay + 90 days post-discharge *(N infection = 59; N no infection = 529)*	Total costs (£)	13,620 (7,762)	7,584 (4,622; p<0.001)	11,869 (10,364, 13,593)	7,480 (7,160, 7,813)	4,389 p<0.001
	LOS (days)	21.9 (21.8)	11.2 (15.2; p<0.001)	16.3 (12.7, 21.0)	9.8 (9.1, 10.7)	6.5 p<0.001
	Readmissions (number)	0.8 (0.8)	0.2 (0.5; p<0.001)	0.7 (0.5, 0.9)	0.2 (0.2, 0.2)	0.5 p<0.001

Time period	Endpoint	Bivariate analysis, mean (SD)		Multivariate analysis, mean (95% CI)		Absolute difference (multivariate analysis)
		Infection	No infection	Infection	No infection	
	Readmissions (rate)	57.6	18.1 (p<0.001)	54.9 (41.1, 68.0)	17.2 (14.1, 20.8)	37.7 p<0.001
	Reoperations (number)	0.3 (0.7)	0.1 (0.3; p<0.05)	0.2 (0.1, 0.3)	0.1 (0.0, 0.1)	0.1 p<0.05
	Reoperations (rate)	15.3	7.0 (p<0.05)	11.1 (5.2, 22.0)	6.1 (4.3, 8.7)	5.0 p=0.1438
Index stay + 1 year post-discharge *(N infection = 72; N no infection = 516)*	Total costs (£)	16,788 (12,914)	8,449 (5,525; p<0.001)	14,597 (12,841, 16,593)	8,294 (7,920, 8,686)	6,303 p<0.001
	LOS (days)	29.2 (34.6)	12.3 (21.1; p<0.001)	22.5 (17.7, 28.5)	10.3 (9.4, 11.2)	12.2 p<0.001
	Readmissions (number)	1.5 (1.6)	0.5 (0.9; p<0.001)	1.5 (1.2, 1.8)	0.5 (0.4, 0.6)	1.0 p<0.001
	Readmissions (rate)	75.0	35.5 (p<0.001)	75.0 (63.6, 83.8)	35.3 (31.2, 39.6)	39.7 p<0.001
	Reoperations (number)	0.6 (0.9)	0.2 (0.5; p<0.01)	0.5 (0.4, 0.7)	0.2 (0.2, 0.3)	0.3 p<0.001
	Reoperations (rate)	36.1	21.7 (p<0.05)	37.4 (26.7, 49.5)	20.7 (17.3, 24.5)	16.8 p<0.05
Index stay + 2 years post-discharge *(N infection = 79; N no infection = 509)*	Total costs (£)	18,779 (14,929)	9,611 (6,284; p<0.001)	16,626 (14,664, 18,849)	9,439 (8,998, 9,901),	7,187 p<0.001
	LOS (days)	31.5 (38.1)	13.4 (22.6; p<0.001)	24.6 (19.6, 30.8)	11.3 (10.4, 12.3)	13.3 p<0.001
	Readmissions (number)	2.1 (2.3)	1.0 (1.5; p<0.001)	2.2 (1.9, 2.5)	0.9 (0.8, 1.0)	1.3 p<0.001
	Readmissions (rate)	77.2	51.1 (p<0.001)	77.6 (67.0, 85.6)	51.4 (46.9, 55.8)	26.3 p<0.001
	Reoperations (number)	0.8 (1.1)	0.4 (0.7; p<0.01)	0.8 (0.6, 1.0)	0.4 (0.3, 0.5)	0.4 p<0.001

Time period	Endpoint	Bivariate analysis, mean (SD)		Multivariate analysis, mean (95% CI)		Absolute difference (multivariate analysis)
		Infection	No infection	Infection	No infection	
	Reoperations (rate)	46.8	32.4 (p<0.05)	49.0 (37.7, 60.3)	31.2 (27.2, 35.5)	17.7 p<0.05

Abbreviations: CI, confidence interval; LOS, length of stay; NA, not applicable; SD, standard deviation.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5-6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*7:9*
Bias	9	Describe any efforts to address potential sources of bias	9-10
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9-10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9-10
		(*b*) Describe any methods used to examine subgroups and interactions	9-10
		(*c*) Explain how missing data were addressed	9
		(*d*) If applicable, explain how loss to follow-up was addressed	10
		(*e*) Describe any sensitivity analyses	9-10
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10:14
		(b) Give reasons for non-participation at each stage	9
		(c) Consider use of a flow diagram	10
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10-11
		(b) Indicate number of participants with missing data for each variable of interest	10:14
		(c) Summarise follow-up time (eg, average and total amount)	10
Outcome data	15*	Report numbers of outcome events or summary measures over time	10:14
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11:14
		(*b*) Report category boundaries when continuous variables were categorized	10:14
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	14-15
Discussion			
Key results	18	Summarise key results with reference to study objectives	15
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	16
Generalisability	21	Discuss the generalisability (external validity) of the study results	15-16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	17

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.