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**Economic outcomes associated with deep surgical site infection in patients with an open fracture of the lower limb**

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## **Abstract**

**Aims:** To estimate economic outcomes associated with deep surgical site infection (SSI) in patients with an open fracture of the lower limb.

**Patients:** 460 UK patients recruited from twenty-four specialist trauma hospitals in the UK Major Trauma Network.

**Methods:** Preference-based health-related quality of life outcomes, assessed using the EuroQol EQ-5D-3L and the SF-6D, and economic costs (£, 2014-15 prices), were measured using participant-completed questionnaires over the 12 months following injury. Descriptive statistics and multivariate regression analysis were used to explore the relationship between deep SSI and health utility scores, quality-adjusted life years (QALYs) and health and personal social service (PSS) costs.

**Results:** Deep SSI was associated with lower EQ-5D-3L derived QALYs (adjusted mean difference - 0.102, 95% CI -0.202 to 0.001, p-value = 0.047) and increased health and social care costs (adjusted mean difference £1,950; 95%CI £1,383 to £5,285, p-value = 0.250) compared to patients without deep SSI over the 12 months following injury.

**Conclusion:** Deep SSI may lead to significantly impaired health-related quality of life and increased economic costs. Our economic estimates can be used to inform clinical and budgetary service planning, and can act as data inputs into future economic evaluations of preventive or treatment interventions.

## Introduction

Fractures of the lower limb are significant injuries, which have long term consequences for patients. Of particular importance are open fractures. These injuries represent a major challenge to reconstructive trauma teams. In the lower limb, the tibia is most often affected <sup>1</sup>. This reflects its paucity of soft tissue coverage. Treatment of the contamination and bone exposure is at the forefront of the orthoplastic paradigm <sup>2</sup>.

The growing expertise and centralisation of care pathways in major trauma networks has done much to improve care for these patients. Yet complications are a common occurrence in open lower limb fractures <sup>3</sup>. Foremost among them is deep infection. The catastrophic consequences of deep infection in fractures are well characterised <sup>4</sup>. Non-union, soft tissue coverage failure, systemic deterioration and diminished rehabilitation all add to the burden of misery for patients. Treatment for deep infection requires further surgery and extensive courses of antibiotics <sup>5</sup>. Even with salvage procedures such as amputation there are no guarantees of success <sup>6</sup>.

The nature of the deep infection as both a complication and disease to be treated make it a resource intensive problem <sup>7,8</sup>. The burden is borne foremost by the patient. This may be psychological, financial, social and physical. The healthcare system in treating patients with deep infection is also burdened. Extensive inpatient stays, multiple procedures and outpatient visits may contribute significantly to the economic cost of caring for these patients.

Attempts to understand the economic costs associated with deep infection after open fractures are limited <sup>7,8</sup>. We are not aware of any such analysis undertaken in the UK healthcare system. However, this is a critical area of study. Deep infection after any surgery is significant for the patient and treating centre. By quantifying the economic costs associated with this complication, efforts to reduce infection by devices, medical treatments and pathways can be justified and contextualised.

The Wound in Open Lower Limb Fracture (WOLLF) trial sought to assess the effectiveness of negative pressure wound therapy (NPWT) in patients with open lower limb fractures<sup>9</sup>. Negative pressure wound therapy is a device used to manage the soft tissue defects associated with open fracture, among other indications. A major part of the trial examined the cost-effectiveness as well as the clinical effectiveness of the device. This involved collecting detailed information around complications, on-going treatment and care needs. The trial-based health economic analysis collected data on economic costs to the health and social care systems and to patients, as well as data on preference-based health-related quality of life measures recommended for cost-effectiveness purposes. This study used these trial data to explore the health economic implications of deep infection after open fracture.

## **Methods**

This study used data from the WOLLF study, a prospective randomised controlled trial that was embedded in the UK Major Trauma Network. The design and methods of WOLLF are described in detail elsewhere.<sup>10</sup> Briefly, the trial recruited adult patients with open fractures of the lower limb graded as Gustilo-Anderson two or above, all of whom were treated in a Major UK Trauma Centre or Trauma Unit with joint orthopaedic and plastic surgical care.<sup>11</sup> Patients were stratified by centre and Gustilo-Anderson grade.

The data set used for this secondary analysis included all 460 participants in the WOLLF study, regardless of trial allocation. Two groups of patients were compared, those without and those with a diagnosis of deep SSI. Deep SSI was defined according to the Centres for Disease Control (CDC) definition.<sup>12</sup> The CDC definition covers the first 30 days following surgery, unless an implant is in place in which case the follow up period is extended to 12 months. Deep SSI presenting within 12

months of the injury and any wound infection requiring continuing medical or surgical intervention after 30 days, including those leading to amputation, were also recorded as a deep SSI. In the WOLLF study, wounds were assessed and medical records reviewed at hospital discharge, or in the case of discharge before 30 days, at the first outpatient appointment (between 30 days and six weeks post-injury as per standard UK clinical practice). Wounds were observed directly and research staff recorded the characteristics of any infection.

Two sets of long-term economic consequences were measured within the WOLLF study: preference-based health-related quality of life outcomes and economic costs. The WOLLF study collected data based on two preference-based health-related quality of life instruments, namely the EuroQoL EQ-5D-3L and the SF-6D, based on participant completion of the EQ-5D-3L and SF-12 measures at baseline and at 3, 6, 9 and 12 months post-randomisation.<sup>13, 14</sup> Responses to the EQ-5D-3L descriptive system covering five dimensions (mobility, self-care, usual activities, pain and anxiety/depression) each with three severity levels (no problems, some or moderate problems, severe or extreme problems) were converted into health utility scores at each time point using the Dolan et al. UK algorithm, generating health utility scores ranging from -0.594 to 1.0.<sup>15</sup> Responses to the SF-12 descriptive system covering eight health concepts (physical functioning, role limitations – physical, bodily pain, general health, vitality, social functioning, role limitations – emotional, mental health) were converted into SF-6D health utility scores at each time point using the Brazier et al. UK algorithm, generating health utility scores ranging from 0.345 to 1.0.<sup>16</sup> Using each measure, quality-adjusted life year (QALY) profiles were generated for each participant over the one year follow-up period, calculated as the area under the curve with linear interpolation. QALYs provide a “measure of the state of health of a person or group in which the benefits, in terms of length of life, are adjusted to reflect the quality of life. One QALY is equal to 1 year of life in perfect health”<sup>17</sup>.

Economic costs were measured using participant-completed questionnaires at each time point, encompassing utilisation of hospital inpatient services, hospital outpatient services, community health and social care, medication use, and aids and adaptations. Resource inputs were valued using

primary and secondary cost sources. Costs were calculated for the initial period of hospitalisation, the period between hospital discharge and three months post-randomisation, and subsequently for each three month time period up to one year post-randomisation. Cumulative total costs were calculated from a UK National Health Service (NHS) and personal social services (PSS) perspective in accordance with national methodological guidance.<sup>18</sup> Costs are reported in British pound sterling using 2015 prices.

Differences at each time point in mean utility values and mean NHS and PSS costs, and differences in EQ-5D and SF-6D derived QALYs and cumulative NHS and PSS costs for the one year follow-up period, were estimated using Student's t-tests. Linear regression models were estimated using ordinary least squares (OLS), with total NHS and PSS costs over each follow-up period regressed on age, gender, trial site, Gustilo-Anderson wound grade, diabetes diagnosis, height, weight and smoker. Whilst age and gender are standard controls, trial site was included to capture any differences in treatment between trial sites, wound grade to capture differences in the severity of the injury and the remaining covariates to capture potential differences in immune response which may regulate the impact of deep SSI. The same set of covariates was used with QALY estimates as the dependent variables, but with additional controls for baseline health utility values. The OLS estimator was selected in preference to a generalised linear model with alternative distributional families and link functions on the basis of Akaike information criterion statistics.<sup>19</sup> The baseline analysis was completed using multiply imputed data, with a complete case analysis included as a sensitivity analysis.

## **Results**

Table 1 summarises the demographic and clinical characteristics of the study population at baseline. The study population was comprised of 460 individuals, 35 of whom had deep SSI, 423 did not, with 2 missing values. In the deep SSI group, the average age was 45 years, compared to 43 years in those

without deep SSI. Males comprised 74% of each group. The proportion of those with diabetes was slightly higher in those with deep SSI, at 11%, compared to 6% in those without. There was also a higher proportion of smokers in the deep SSI group, 46%, compared to 32% in those without.

Table S1 of the accompanying supplementary information file summarises the mean EQ-5D utility scores and SF-6D utility scores for each group, at each timepoint, and reports tests of statistical significance for differences between mean utility scores in each group. Similarly, QALYs calculated over the one year follow-up period (using either EQ-5D or SF-6D utility scores) and NHS and PSS costs over each time period (initial hospitalisation and subsequent period to three months post-randomisation, 3-6 months, 6-9 months, 9-12 months, 0-12 months) and for each cost category (hospital inpatient care, hospital outpatient care, community health and social care, medications, aids and adaptations) are reported together with tests of statistical significance for differences in values.

Differences were found between EQ-5D-3L utility scores at 6 months (0.14 higher in those without deep SSI,  $p=0.038$ ), 12 months (0.16 higher in those without deep SSI,  $p=0.023$ ), as well as in EQ-5D-3L QALYs calculated over the one year follow-up period (0.16 higher in those without deep SSI,  $p=0.01$ ). However, these results were not replicated for the SF-6D.

Regarding economic costs, hospital inpatient costs in the 3-6 month time period were higher in the deep SSI group (£2692 v £691,  $p=0.049$ ). Total NHS and PSS costs were higher in the deep SSI group over the 0-6 month (£15598 v £12304,  $p=0.099$ ) and 3-6 month (£3542 v £1597,  $p=0.095$ ) time periods. However, total NHS and PSS costs were higher in the group without deep SSI in the 6-9 month time period (£1091 v £623,  $p=0.068$ ).

Table 2 details the results of the multivariate analyses based on multiple imputation of missing data, considering the effects of deep SSI on total NHS and PSS costs over each follow-up period, as well as on QALYs calculated using either EQ-5D-3L or SF-6D utility scores over the one year follow-up period. Using multiply imputed data, there was a statistically significant difference in QALYs calculated using



EQ-5D-3L utility scores at the 5% significance level ( $p=0.047$ ). Results based on analysis of complete cases are presented in Table S2 of the supplementary file for completeness. Considering the complete case analysis, deep SSI was not a statistically significant predictor of a difference in QALYs calculated using the EQ-5D-3L at the 5% significance level ( $p=0.079$ ). For both the multiple imputation and complete case analyses, deep SSI was not found to have a statistically significant association with total NHS and PSS costs over any of the time periods considered or with SF-6D generated QALYs calculated over the one year follow-up period.

## **Discussion**

This study is the first, to our knowledge, to assess the economic outcomes associated with deep surgical site infection in patients with an open fracture of the lower limb. The use of high quality prospectively collected data is a major strength of this study. This is very relevant to open fracture populations who typically have very poor long-term follow up rates. Another major strength is the multicentre source of patients. This is critical as it improves the generalisability of the findings across health care settings, particularly within the UK NHS.

The total number of patients with deep infection ( $n=35$ ) is relatively small. This means that the summative analyses here can be influenced by a few clinical events or treatments. Furthermore follow up is limited to 12 months. Other studies have shown that the consequences of complications after open fracture persist well after this window<sup>20</sup>, and therefore our estimates can be viewed as conservative assessments of the long-term economic implications of deep surgical site infection in patients with an open fracture of the lower limb.

Other studies have considered complications following lower limb injury. Chung and colleagues studied over 500 major lower limb injuries and assessed the cost implications as part of the Lower Extremity Assessment Project (LEAP) <sup>7</sup>. The LEAP patient cohort was similar to the WOLLF cohort, but was not limited to open fractures. However, the LEAP analysis was undertaken from a healthcare provider perspective only <sup>21</sup>. In turn, the healthcare context for the LEAP analysis is highly different to the UK NHS and no specific economic analysis was undertaken of the infected cases. The LEAP findings have been replicated in other studies of severe lower limb injury <sup>22</sup>.

In our study, there was a statistically significant difference in EQ-5D-3L QALYs generated over the one year follow-up period. Whilst this finding was not replicated for the SF-6D, the overall difference in SF-6D utility score at 12 months exceeds the 0.03 minimally important clinical difference (12). As is intuitive, economic costs were higher in the deep SSI group at 12 months. These costs were borne both by the NHS and social care systems and by patients and their carers. The difference in total NHS and PSS costs over the 12 month follow-up period was estimated at £1242. This figure may be of benefit to clinical and budgetary service planning. More generally, the economic estimates generated by this analysis can act as data inputs into future economic evaluations of preventive or treatment interventions.

In conclusion, the entirely expected finding of higher economic costs within the deep infection cohort should empower the clinician to be aggressive with identifying infection expeditiously and being as rigorous as possible in reducing infection. When viewed in conjunction with our findings on preference-based health-related quality of life outcomes, our estimates are important too for the patient who can now be informed that deep surgical site infection in open fractures of the lower limb will have considerable long term consequences through which they will need significant support.

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## References

1. Giannoudis PV, Papakostidis C, Roberts C. A review of the management of open fractures of the tibia and femur. *The Journal of Bone and Joint Surgery British volume* 2006; **88-B**(3): 281-9.
2. NICE. Fractures (complex): assessment and management - NICE guideline [NG37]. Available from <https://www.nice.org.uk/guidance/ng37>, 2016.
3. Babhulkar S, Raza HKT. Open fractures. *Indian Journal of Orthopaedics* 2008; **42**(4): 365-7.
4. Struijs PAA, Poolman RW, Bhandari M. Infected Nonunion of the Long Bones. *Journal of Orthopaedic Trauma* 2007; **21**(7): 507-11.
5. Rightmire E, Zurakowski D, Vrahas M. Acute Infections After Fracture Repair: Management With Hardware in Place. *Clinical Orthopaedics and Related Research* 2008; **466**(2): 466-72.
6. Bose D, Kugan R, Stubbs D, McNally M. Management of infected nonunion of the long bones by a multidisciplinary team. *The Bone & Joint Journal* 2015; **97-B**(6): 814-7.
7. Chung KC, Saddawi-Konefka D, Haase SC, Kaul G. A Cost-Utility Analysis of Amputation versus Salvage for Gustilo IIIB and IIIC Open Tibial Fractures. *Plastic and reconstructive surgery* 2009; **124**(6): 1965-73.
8. Mackenzie E, Snow Jones A, J Bosse M, et al. Health-Care Costs Associated with Amputation or Reconstruction of a Limb-Threatening Injury; 2007.
9. Costa ML, Achten J, Bruce J, et al. Effect of negative pressure wound therapy vs standard wound management on 12-month disability among adults with severe open fracture of the lower limb: The wolff randomized clinical trial. *JAMA* 2018; **319**(22): 2280-8.
10. Achten J, Parsons NR, Bruce J, et al. Protocol for a randomised controlled trial of standard wound management versus negative pressure wound therapy in the treatment of adult patients with an open fracture of the lower limb: UK Wound management of Open Lower Limb Fractures (UK WOLFF). *BMJ Open* 2015; **5**(9).
11. Gustilo RB, Anderson JT. Prevention of infection in the treatment of one thousand and twenty-five open fractures of long bones: retrospective and prospective analyses. *J Bone Joint Surg Am* 1976; **58**(4): 453-8.
12. Horan TC, Gaynes RP, Martone WJ, Jarvis WR, Emori TG. CDC definitions of nosocomial surgical site infections, 1992: a modification of CDC definitions of surgical wound infections. *Infect Control Hosp Epidemiol* 1992; **13**(10): 606-8.
13. EuroQol Group. EuroQol: a new facility for the measurement of health-related quality of life. *Health Policy* 1990; **16**(3): 199-208.
14. Ware J, Jr., Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. *Med Care* 1996; **34**(3): 220-33.
15. Dolan P. Modeling valuations for EuroQol health states. *Med Care* 1997; **35**(11): 1095-108.
16. Brazier JE, Roberts J. The estimation of a preference-based measure of health from the SF-12. *Med Care* 2004; **42**(9): 851-9.
17. NICE. Glossary: Quality-adjusted life year. Available online from <https://www.nice.org.uk/glossary?letter=q>. Accessed 04 July 2018, 2018.
18. National Institute for Health and Care Excellence. Guide to the methods of technology appraisal 2013. (accessed 14/01/2016).
19. Glick HA, Doshi JA, Sonnad SS, Polsky D. Economic Evaluation in Clinical Trials: Oxford University Press; 2014.
20. Saddawi-Konefka D, Kim HM, Chung KC. A Systematic Review of Outcomes and Complications of Reconstruction and Amputation for Type IIIB and IIIC Fractures of the Tibia. *Plastic and reconstructive surgery* 2008; **122**(6): 1796-805.
21. Pollak AN, Jones AL, Castillo RC, Bosse MJ, MacKenzie EJ, the LSG. The Relationship Between Time to Surgical Débridement and Incidence of Infection After Open High-Energy Lower Extremity Trauma. *The Journal of Bone and Joint Surgery American volume* 2010; **92**(1): 7-15.

22. MacKenzie EJ, Jones AS, Bosse MJ, et al. Health-care costs associated with amputation or reconstruction of a limb-threatening injury. *J Bone Joint Surg Am* 2007; **89**(8): 1685-92.