Infection after total joint replacement of the hip and knee: research programme including the INFORM RCT

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his institution receives market-rate payment for this teaching from DePuy Synthes (Raynham, MA, USA). He is a co-applicant on a grant from Stryker Corporation investigating the outcome of the Triathlon total knee replacement. He is a member of the National Joint Registry lot 2 contract (statistical analysis) team. He is NIHR Clinical Research Network West of England lead for Trauma and Emergencies, a member of the NIHR Bristol Biomedical Research Centre and principal investigator on two NIHR Health Technology Assessment grants (NIHR129011 and NIHR127849).

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Scientific summary

Research programme including the INFORM RCT

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Scientific summary

Background

For many people, total joint replacement is a highly successful treatment for osteoarthritis, hip fracture and other joint conditions, leading to a reduction in pain and an improvement in physical function. However, a small number of patients experience serious adverse events, of which deep prosthetic joint infection is considered the most serious. If untreated, infection can result in severe pain, disability and death. Most patients are treated with a two-stage revision procedure involving two separate operations. An alternative single-stage procedure is also used. To our knowledge, the effectiveness of single-stage revision has not been compared with that of the two-stage procedure in a randomised trial.

Objectives

In the INFORM (INFection ORthopaedic Management) programme, our aim was to produce knowledge about risk factors, patient and surgeon experiences, and how best to treat prosthetic joint infection after total joint replacement. Ultimately, the programme aimed to identify ways of improving outcomes for patients with prosthetic joint infection.

The specific objectives were to:

- explore the implications of prosthetic joint infection for patients and health care
- describe the experiences of patients with prosthetic joint infection and their treating surgeons
- identify the risk factors for prosthetic joint infection
- evaluate new methods for diagnosis of prosthetic joint infection
- compare the effectiveness of surgical treatments for prosthetic joint infection over 18 months and their cost-effectiveness from two perspectives: a health-care provider and Personal Social Services perspective, and a societal perspective
- explore patient preferences for revision procedures.

Methods

Defined by methodology, we conducted seven work packages:

- Work package 1 – we conducted systematic literature reviews of treatment strategies for prosthetic joint infection after total hip and knee joint replacement, and a meta-analysis of individual patient data to compare reinfection outcomes after single- and two-stage revision surgery. We also reviewed risk factors, diagnostic methods and costs.
- Work package 2 – we performed an analysis of the National Joint Registry (NJR) to identify predictors of prosthetic joint infection after total hip or knee replacement and compare care according to different health-care characteristics.
- Work package 3 – through qualitative interviews we assessed the impact on patients of prosthetic joint infection and treatment strategies, and surgeons' views on treatment.

- Work package 4 – in a randomised controlled trial (RCT) with embedded qualitative interviews, we investigated whether or not treating prosthetic joint infection after total hip replacement with a single-stage revision rather than the traditionally used two-stage revision improved patients' quality of life and was cost-effective.
- Work package 5 – in analyses of the NJR and Hospital Episode Statistics, we assessed the economic implications of prosthetic joint infection. We also conducted an economic evaluation within the RCT.
- Work package 6 – by developing and applying a discrete choice questionnaire, we assessed the trade-offs that patients are willing to make between patient-reported and clinical outcomes, and explored the degree to which treatment strategies change preferences for those outcomes.
- Work package 7 – finally, we disseminated findings to patients, members of the public, clinicians and stakeholders.

Patient and public involvement

The development of the programme and the conduct of the work packages was underpinned by patient and public involvement. Within the programme, our patient forum contributed to the design of patient recruitment and information literature, research processes and questionnaires, the identification of outcomes of importance to patients, and dissemination strategies.

Results

Implications of prosthetic joint infection for health care

The rates of infection after joint replacement vary across different care settings. Typically, in northern Europe, about 1% of people will experience a prosthetic joint infection within 2 years of their primary hip or knee replacement. Our analyses of UK registry data showed that rates of revision surgery for prosthetic joint infection were 0.26% [95% confidence interval (CI) 0.24% to 0.27%] and 0.32% (95% CI 0.31% to 0.34%), respectively, within 2 years of primary hip and knee replacement and 0.62% (95% CI 0.59% to 0.65%) and 0.75% (95% CI 0.72% to 0.78%), respectively, at 10 years. Revision rates for prosthetic joint infection after aseptic revision surgery were about four times those after primary hip or knee replacement.

In 2014, the treatment of prosthetic joint infection after hip and knee replacements was with a two-stage procedure in about 61% and 75% of patients, respectively, but the use of single-stage revision had increased during the previous 10 years.

In published studies, the cost of treating prosthetic joint infection was about four times that of primary hip or knee replacement. No robust information was identified comparing costs of single- and two-stage revision strategies. In our registry analysis, health-care costs in the 5 years after primary hip replacement were five times greater for people with prosthetic joint infection than for people with no infection. The average cost of inpatient and day-case admissions was £41,633 (95% CI £39,079 to £44,187) for patients with hip prosthetic joint infection and £8181 (95% CI £7614 to £8748) for those with no infection, a difference in cost of £33,452 (95% CI £30,828 to £36,077).

Limitations to the registry studies were that we were only able to report the outcome of revision for treatment of prosthetic joint infection and do not know how many people were treated without surgery. Resources included in cost calculations in the studies we reviewed varied considerably, and in our registry analysis we did not consider costs relating to outpatient, primary and community care, prescribed medications and treatments received outside England.

Patient and surgeon experience

Overall, we conducted semistructured qualitative interviews with 67 patients with hip or knee prosthetic joint infection and with 35 experienced surgeons at 12 large centres in England and Wales. Patients

described the devastating effects of prosthetic joint infection during the periods of symptom onset, treatment and protracted recovery. Patients were frequently dissatisfied with the provision of information and physiotherapy and expressed a need for more psychological and rehabilitative support during treatment and long-term recovery.

A two-stage revision procedure for hip prosthetic joint infection with or without a cement spacer had a greater negative impact on people's well-being than a single-stage procedure or two-stage revision with a custom-made articulating spacer (CUMARS). Patients receiving single- or two-stage revision with a CUMARS reported earlier mobilisation and better functional outcomes, but those in the two-stage revision group perceived that recovery was slow. The use of a cement spacer was associated with increased pain.

In qualitative interviews, surgeons described that prosthetic joint infection caused a significant emotional impact. They highlighted the importance of a supportive multidisciplinary team.

Although data saturation was achieved in the qualitative studies, a limitation of our research was that the subgroups were small.

Risk factors for prosthetic joint infection

Systematic reviews identified that male sex, high body mass index and diabetes were risk factors for prosthetic joint infection, and these were confirmed in joint registry analyses.

New risk factors were identified in our registry analyses, including dementia, which was associated with an increased risk of early prosthetic joint infection. People with more comorbidities and some specific conditions were at greater risk of infection.

There was no consistent evidence linking health-care setting and surgeon experience with prosthetic joint infection, but there was a suggestion that the posterior approach in hip replacement and the use of ceramic-on-ceramic and ceramic-on-polyethylene bearings in knee replacement were associated with lower risks of infection. Infection rates were lower in people receiving uncemented implants.

With observational data, a limitation is that we cannot establish whether or not relationships between risk factors and revision for prosthetic joint infection are causal.

Diagnosis of prosthetic joint infection

In our systematic review of contemporary synovial biomarkers, alpha-defensin and leucocyte esterase showed high diagnostic accuracy for prosthetic joint infection. The costly alpha-defensin test was extremely sensitive and specific in the identification of prosthetic joint infection.

A limitation was that only a small number of studies were identified, and several were conducted by a research group holding patents for related products.

Reinfection outcomes after single- or two-stage revision of prosthetic joint infection

Although systematic reviews and individual patient data meta-analysis showed similar reinfection outcomes for patients treated with single-stage revision and those treated with two-stage revision, registry analyses showed a higher rate of rerevision for infection early after single-stage revision. However, overall, 41% and 45% fewer operations were received by patients treated initially with a single-stage procedure for prosthetic joint infection of the hip and knee, respectively, than required in a two-stage procedure.

A limitation of these studies is that patients may have been selected for joint replacement and specific treatments based on their health status and the infecting organism.

In another meta-analysis, debridement, antibiotics and implant retention was effective in > 60% of cases, particularly if carried out early.

Patient outcomes after single- or two-stage revision of hip prosthetic joint infection

The INFORM trial was a multicentre, two-arm, parallel group, participant- and observer-unblinded, randomised superiority trial comparing single- and two-stage revision for hip prosthetic joint infection. Between March 2015 and December 2018, 140 patients were recruited from hospitals in England (11 sites), Wales (one site) and Sweden (three sites). Eligible patients had a clinical diagnosis of hip prosthetic joint infection requiring revision surgery. Eighteen months was chosen as the timing for the primary outcome as maximum recovery from all surgeries should have been achieved and further health improvements after this time would be unlikely.

At 3 months, participants who received a single-stage procedure had less pain and improved function compared with those receiving two-stage revision, but there was no difference at 18 months. The occurrence of complications including reinfection, rehospitalisation or reoperation as a result of the surgical management were similar between the groups.

A limitation of the INFORM RCT was that it was not statistically powered for reinfection outcome.

Cost-effectiveness of single- or two-stage revision of hip prosthetic joint infection

In the INFORM trial, people randomised to a single-stage procedure had lower costs and higher quality-adjusted life-years than those randomised to a two-stage procedure. The two hospital stays involved with a two-stage procedure led to a higher cost in this group. The greater use of district nurse home visits and home care worker visits indicates that patients in this group were also less able to self-care and leave their home at this time. The within-trial economic evaluation showed that the single-stage procedure is the cost-effective option for patients with hip prosthetic joint infection.

Patient preferences for single- or two-stage revision of hip prosthetic joint infection

To quantify the surgical preferences of patients with hip prosthetic joint infection, we developed a discrete choice questionnaire with attributes identified in our qualitative studies. Questionnaires were completed at 18 months after randomisation by 57 patients in the INFORM randomised trial. The most valued characteristics in decisions about revision surgery for hip prosthetic joint infection were the ability to engage in valued activities and the time taken to return to normal activity. Less valued but important preferences were for few or no side effects from antibiotics, and only one operation.

This study had some limitations. Feedback from the first participants suggested that the questionnaire was difficult to complete. However, altering the instructions and format and providing nurse support allowed participants to understand and complete the questionnaire. The sample size was too small to explore responses in subgroups.

Conclusions: implications for health care

In the INFORM programme we identified risk factors, effective treatments and patient preferences for the treatment of prosthetic joint infection. Risk factors include male sex, diagnoses other than osteoarthritis, comorbidities including diabetes, liver disease and dementia, and surgical factors such as use of the lateral approach. Infection is devastating for patients and surgeons. Patients have a preference for treatments that allow full functional return within 3–9 months. Patients highlighted the need for greater support at all stages of treatment. Debridement, antibiotics and implant retention is effective in > 60% of cases, particularly if it is carried out early. For infected hip replacements, single- and two-stage revision appear equally efficacious, but single-stage revision has better early results and is more cost-effective.

Recommendations for research

- Develop clear information for people receiving treatments for prosthetic joint infection.
- Develop, implement and evaluate enhanced care pathways for people with prosthetic joint infection.
- Develop counselling, peer support and supportive interventions in the revision surgery pathway and improve physiotherapy provision for patients with prosthetic joint infection.
- Explore whether or not patient education and supportive care can enable earlier recognition of signs and symptoms of infections.
- Investigate the preparedness for adverse outcomes, help-seeking and information for health-care professionals about the early signs of and care for prosthetic joint infection.
- Develop preventative strategies for high-risk patients.
- Explore the effectiveness of counselling, monitoring and preventative strategies.
- Explore the long-term survival of CUMARSs.
- Appraise the role of spacers in two-stage revisions.
- Conduct a randomised trial of treatments for knee prosthetic joint infection.
- Make independent UK comparisons between synovial fluid alpha-defensin, leucocyte esterase and traditional diagnostic tests.
- Establish a set of diagnostic criteria relevant to contemporary NHS practice.

Study registration

The INFORM RCT is registered as ISRCTN10956306. All systematic reviews were registered in PROSPERO (as CRD42017069526, CRD42015023485, CRD42018106503, CRD42018114592, CRD42015023704, CRD42017057513, CRD42015016559, CRD42015017327 and CRD42015016664).

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