UNIVERSITY OF BRISTOL

University of Bristol - Explore Bristol Research
General rights

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

Ashley W Blom, Andrew D Beswick, Amanda Burston, Fran E Carroll, Kirsty Garfield, Rachael Gooberman-Hill, Shaun Harris, Setor K Kunutsor, Athene Lane, Erik Lenguerrand, Alasdair MacGowan, Charlotte Mallon, Andrew J Moore, Sian Noble, Cecily K Palmer, Ola Rolfson, Simon Strange and Michael R Whitehouse on behalf of the INFORM group

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

Ashley W Blom,[1,2]* Andrew D Beswick,[2]
Amanda Burston,[2] Fran E Carroll,[3] Kirsty Garfield,[3,4]
Rachael Gooberman-Hill,[2] Shaun Harris,[3,4]
Setor K Kunutsor,[1,2] Athene Lane,[3,4]
Erik Lenguerrand,[2] Alasdair MacGowan,[5]
Charlotte Mallon,[2] Andrew J Moore,[2]
Sian Noble,[3] Cecily K Palmer,[3,6] Ola Rolfson,[2,7]
Simon Strange[2] and Michael R Whitehouse[1,2]
on behalf of the INFORM group

[1]National Institute for Health and Care Research Bristol Biomedical Research Centre, University Hospitals Bristol and Weston NHS Foundation Trust and University of Bristol, Bristol, UK
[2]Musculoskeletal Research Unit, Translational Health Sciences, Bristol Medical School, University of Bristol, Bristol, UK
[3]Population Health Sciences, Bristol Medical School, University of Bristol, Bristol, UK
[4]Bristol Randomised Trials Collaboration, University of Bristol, Bristol UK
[5]Department of Medical Microbiology, Southmead Hospital, Bristol, UK
[6]National Institute for Health and Care Research Applied Research Collaboration West (NIHR ARC West), University Hospitals Bristol NHS Foundation Trust and University of Bristol, Bristol, UK
[7]Department of Orthopaedics, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

*Corresponding author

Programme Grants for Applied Research

> **Criteria for inclusion in the *Programme Grants for Applied Research* journal**
> Reports are published in *Programme Grants for Applied Research* (PGfAR) if (1) they have resulted from work for the PGfAR programme, and (2) they are of a sufficiently high scientific quality as assessed by the reviewers and editors.

Programme Grants for Applied Research programme

The Programme Grants for Applied Research (PGfAR) programme, part of the National Institute for Health and Care Research (NIHR), was established in 2006 to fund collaborative, multidisciplinary programmes of applied research to solve health and social care challenges. Findings are expected to provide evidence that lead to clear and identifiable patient benefits, in the relatively near future.

PGfAR is researcher led and does not specify topics for research; however, the research must be in an area of priority or need for the NHS and the social care sector of the Department of Health and Social Care, with particular emphasis on health and social care areas that cause significant burden, where other research funders may not be focused, or where insufficient funding is available.

The programme is managed by the NIHR Central Commissioning Facility (CCF) with strategic input from the Programme Director. For more information about the PGfAR programme please visit the website: https://www.nihr.ac.uk/explore-nihr/funding-programmes/programme-grants-for-applied-research.htm

This report

Abstract

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

Ashley W Blom,[1,2]* Andrew D Beswick,[2] Amanda Burston,[2] Fran E Carroll,[3] Kirsty Garfield,[3,4] Rachael Gooberman-Hill,[2] Shaun Harris,[3,4] Setor K Kunutsor,[1,2] Athene Lane,[3,4] Erik Lenguerrand,[2] Alasdair MacGowan,[5] Charlotte Mallon,[2] Andrew J Moore,[2] Sian Noble,[3] Cecily K Palmer,[3,6] Ola Rolfson,[2,7] Simon Strange[2] and Michael R Whitehouse[1,2] on behalf of the INFORM group

[1]National Institute for Health and Care Research Bristol Biomedical Research Centre, University Hospitals Bristol and Weston NHS Foundation Trust and University of Bristol, Bristol, UK
[2]Musculoskeletal Research Unit, Translational Health Sciences, Bristol Medical School, University of Bristol, Bristol, UK
[3]Population Health Sciences, Bristol Medical School, University of Bristol, Bristol, UK
[4]Bristol Randomised Trials Collaboration, University of Bristol, Bristol UK
[5]Department of Medical Microbiology, Southmead Hospital, Bristol, UK
[6]National Institute for Health and Care Research Applied Research Collaboration West (NIHR ARC West), University Hospitals Bristol NHS Foundation Trust and University of Bristol, Bristol, UK
[7]Department of Orthopaedics, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

*Corresponding author Ashley.Blom@bristol.ac.uk

Background: People with severe osteoarthritis, other joint conditions or injury may have joint replacement to reduce pain and disability. In the UK in 2019, over 200,000 hip and knee replacements were performed. About 1 in 100 replacements becomes infected, and most people with infected replacements require further surgery.

Objectives: To investigate why some patients are predisposed to joint infections and how this affects patients and the NHS, and to evaluate treatments.

Design: Systematic reviews, joint registry analyses, qualitative interviews, a randomised controlled trial, health economic analyses and a discrete choice questionnaire.

Setting: Our studies are relevant to the NHS, to the Swedish health system and internationally.

Participants: People with prosthetic joint infection after hip or knee replacement and surgeons.

Interventions: Revision of hip prosthetic joint infection with a single- or two-stage procedure.

Main outcome measures: Long-term patient-reported outcomes and reinfection. Cost-effectiveness of revision strategies over 18 months from two perspectives: health-care provider and Personal Social Services, and societal.

ABSTRACT

Data sources: National Joint Registry; literature databases; published cohort studies; interviews with 67 patients and 35 surgeons; a patient discrete choice questionnaire; and the INFORM (INFection ORthopaedic Management) randomised trial.

Review methods: Systematic reviews of studies reporting risk factors, diagnosis, treatment outcomes and cost comparisons. Individual patient data meta-analysis.

Results: In registry analyses, about 0.62% and 0.75% of patients with hip and knee replacement, respectively, had joint infection requiring surgery. Rates were four times greater after aseptic revision. The costs of inpatient and day-case admissions in people with hip prosthetic joint infection were about five times higher than those in people with no infection, an additional cost of > £30,000. People described devastating effects of hip and knee prosthetic joint infection and treatment. In the treatment of hip prosthetic joint infection, a two-stage procedure with or without a cement spacer had a greater negative impact on patient well-being than a single- or two-stage procedure with a custom-made articulating spacer. Surgeons described the significant emotional impact of hip and knee prosthetic joint infection and the importance of a supportive multidisciplinary team. In systematic reviews and registry analyses, the risk factors for hip and knee prosthetic joint infection included male sex, diagnoses other than osteoarthritis, high body mass index, poor physical status, diabetes, dementia and liver disease. Evidence linking health-care setting and surgeon experience with prosthetic joint infection was inconsistent. Uncemented fixation, posterior approach and ceramic bearings were associated with lower infection risk after hip replacement. In our systematic review, synovial fluid alpha-defensin and leucocyte esterase showed high diagnostic accuracy for prosthetic joint infection. Systematic reviews and individual patient data meta-analysis showed similar reinfection outcomes in patients with hip or knee prosthetic joint infection treated with single- and two-stage revision. In registry analysis, there was a higher rate of early rerevision after single-stage revision for hip prosthetic joint infection, but, overall, 40% fewer operations are required as part of a single-stage procedure than as part of a two-stage procedure. The treatment of hip or knee prosthetic joint infection with early debridement and implant retention may be effective in > 60% of cases. In the INFORM randomised controlled trial, 140 patients with hip prosthetic joint infection were randomised to single- or two-stage revision. Eighteen months after randomisation, pain, function and stiffness were similar between the randomised groups ($p = 0.98$), and there were no differences in reinfection rates. Patient outcomes improved earlier in the single-stage than in the two-stage group. Participants randomised to a single-stage procedure had lower costs (mean difference –£10,055, 95% confidence interval –£19,568 to –£542) and higher quality-adjusted life-years (mean difference 0.06, 95% confidence interval –0.07 to 0.18) than those randomised to a two-stage procedure. Single-stage was the more cost-effective option, with an incremental net monetary benefit at a threshold of £20,000 per quality-adjusted life-year of £11,167 (95% confidence interval £638 to £21,696). In a discrete choice questionnaire completed by 57 patients 18 months after surgery to treat hip prosthetic joint infection, the most valued characteristics in decisions about revision were the ability to engage in valued activities and a quick return to normal activity.

Limitations: Some research was specific to people with hip prosthetic joint infection. Study populations in meta-analyses and registry analyses may have been selected for joint replacement and specific treatments. The INFORM trial was not powered to study reinfection and was limited to 18 months' follow-up. The qualitative study subgroups were small.

Conclusions: We identified risk factors, diagnostic biomarkers, effective treatments and patient preferences for the treatment of hip and knee prosthetic joint infection. The risk factors include male sex, diagnoses other than osteoarthritis, specific comorbidities and surgical factors. Synovial fluid alpha-defensin and leucocyte esterase showed high diagnostic accuracy. Infection is devastating for patients and surgeons, both of whom describe the need for support during treatment. Debridement and implant retention is effective, particularly if performed early. For infected hip replacements, single- and two-stage revision appear equally efficacious, but single-stage has better early results, is cost-effective at 18-month follow-up and is increasingly used. Patients prefer treatments that allow full functional return within 3–9 months.

Future work: For people with infection, develop information, counselling, peer support and care pathways. Develop supportive care and information for patients and health-care professionals to enable the early recognition of infections. Compare alternative and new treatment strategies in hip and knee prosthetic joint infection. Assess diagnostic methods and establish NHS diagnostic criteria.

Contents

CONTENTS

CONTENTS

xiv

List of tables

List of figures

List of boxes

List of abbreviations

ASA	American Society of Anesthesiologists	MINORS	methodological index for non-randomized studies
AUC	area under the curve	MOOSE	Meta-analysis Of Observational Studies in Epidemiology
BMI	body mass index	MSIS	Musculoskeletal Infection Society
CEAC	cost-effectiveness acceptability curve	NICE	National Institute for Health and Care Excellence
CHEC-list	Consensus on Health Economic Criteria checklist	NIHR	National Institute for Health and Care Research
CI	confidence interval	NJR	National Joint Registry for England, Wales, Northern Ireland and the Isle of Man
CONSORT	Consolidated Standard of Report Trials		
CUMARS	custom-made articulating spacer	ONS	Office for National Statistics
DAIR	debridement, antibiotics and implant retention	PEP-R	Patient Experience Partnership in Research
EQ-5D-3L	EuroQol-5 Dimensions, three-level version	PPI	patient and public involvement
		PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
EQ-5D-5L	EuroQol-5 Dimensions, five-level version		
HES	Hospital Episode Statistics	PSS	Personal Social Services
HR	hazard ratio	QALY	quality-adjusted life-year
HRG	Healthcare Resource Group	QUADAS-2	Quality Assessment of Diagnostic Accuracy Studies-2
INFORM	INFection ORthopaedic Management	RCT	randomised controlled trial
iNMB	incremental net monetary benefit	RR	relative risk
IPD	individual patient data	WOMAC	Western Ontario and McMasters Universities Osteoarthritis Index
IQR	interquartile range		

Plain English summary

People with severe osteoarthritis, other joint conditions or joint injuries may undergo joint replacement to reduce pain and disability. In the UK in 2019, over 200,000 hip and knee replacements were performed. About 1 in 100 become infected. Treatment usually requires two operations to remove and replace the joint, with antibiotics between surgeries. Some surgeons treat joint infection with one operation.

Our research was needed to find out why some patients are predisposed to getting joint infections and how this affects patients and the NHS, and to evaluate treatments.

We reviewed previous research, analysed a national joint registry, interviewed patients and surgeons to find out their experiences of infection, assessed costs to the NHS and patients, and explored aspects of treatments important to patients. Treatments were compared by randomly allocating 140 patients with hip joint infection to one or two operations and assessing the impact on quality of life and health-care costs. A patient forum supported the research.

We found that, after hip and knee replacement, about 0.62% and 0.75% of patients, respectively, had joint infection requiring surgery. It costs over £30,000 to treat a hip joint infection.

We showed that risk of joint infection is greater in men, people who are overweight and those with pre-existing health conditions, and when some surgical techniques are used. Joint infection is difficult to detect, but new tests of joint fluid show promise. Patients and surgeons described the devastating effects of joint infection. Important concerns for patients were the time taken to recover and engage in valued activities and the need for support and information.

The research we reviewed indicated that hip joint infection treated in one or two operations cleared infection equally, but joint registry analysis raised concern about early problems after treatment with one operation. The randomised trial found that recovery was delayed in people receiving two operations. However, after 18 months, the levels of pain, disability and complications were similar between the groups. The NHS and patient costs were lower when treatment was with one operation.

Scientific summary

Parts of this report have been reproduced or adapted with permission from Blom et al.[1] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) license, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: http://creativecommons.org/licenses/by/4.0/. The text below includes minor additions and formatting changes to the original text.

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

Funding

SYNOPSIS

Background to the INFORM programme

Joint replacement

Osteoarthritis is the most common form of joint disease, affecting nearly 10% of adults in the UK[2] and about 23% of adults in the USA.[3] For people with advanced hip or knee osteoarthritis, as well as those with other joint conditions and injury, joint replacement aims to relieve pain and improve function.

In the UK in 2005, the lifetime risk of receiving a primary hip replacement was estimated to be 12% in women and 7% in men, and for primary knee replacement 11% in women and 8% in men.[4] Internationally, the lifetime risks of hip and knee replacement increased between 2003 and 2013.[5,6] In Spain in 2015, the lifetime risk in patients with osteoarthritis was 14% for hip replacement and 30% for knee replacement.[7]

In the UK in 2019, > 200,000 primary hip and knee replacements were performed to treat diseased or damaged joints[8,9] with about 98% a consequence of osteoarthritis. In the USA in 2020, an estimated 1.6 million hip and knee joints will have required replacement.[10]

Prosthetic joint infection

For many people, joint replacement is a highly successful treatment leading to a reduction in pain and improvement in physical function. However, severe adverse events occur in a small number of patients, including infection, dislocation, fracture, thromboembolism and neurovascular damage.[11–16] Deep prosthetic joint infection is considered the most serious adverse event and, if untreated, can result in severe pain, disability and death.[17]

Prosthetic joint infection occurring within 2 years of joint replacement is mainly surgically acquired[18] and associated with wound inflammation, joint effusion, pain and loss of function.[19] Early infections are commonly caused by virulent bacteria with acute onset of pain, effusion, erythema and fever. Delayed infections typically present with symptoms similar to those after aseptic joint failure.

Bacteria adhere to implants, creating a glycocalyx biofilm and making treatment of established deep infection difficult.[20,21] Bacteria are introduced during the operation or later by haematogenous spread from other infected tissues and attach to the implant surface. Biofilm forms, matures and eventually disperses with spread of infection. Biofilm formation means that treatment with antibiotics alone is rarely effective, and, consequently, deep prosthetic joint infections are difficult to treat.

Deep surgical site infection after orthopaedic procedures has been described as 'an event that inflicted deep suffering and changed the physical, emotional, social and economic aspects of life in extremely negative ways'.[22] People who develop prosthetic joint infection report high levels of pain and disability, and poor mental health and social functioning.[23] Even patients treated successfully have worse quality of life than those with uncomplicated joint replacement.

Incidence of prosthetic joint infection and rate of revision

In December 2019, we searched MEDLINE for cohort studies reporting incidence rates of hip and knee prosthetic joint infection. Fifteen studies were identified (see *Appendix 1*). Methodological quality was assessed, specifically concerns relating to selection bias (inclusion of consecutive patients and representativeness) and missing data (follow-up rate of < 80%).[24] Prospective studies had good follow-up rates. Concerns about generalisability in some studies arose from the inclusion of single centres and the retrospective identification of cases.

Hip prosthetic joint infection

Four studies had no methodological concerns.[25–28] In Finnish and Swedish joint registries, rates of prosthetic joint infection within 2 years of primary hip replacement were about 0.9%.[27,28] In other studies with no methodological concerns, rates of infection ranged from 0.78% within 2 years in a US multicentre cohort[25] to 2.09% within 1 year in national surveillance data in the Republic of Korea.[26] Single-centre UK studies with prospective and retrospective designs reported infection rates of 0.57% at up to 15 years[12] and 1.08% after 8 years,[29] respectively.

Revision for hip prosthetic joint infection

In registry studies from Norway, the UK and Denmark that had no methodological concerns, revision to treat prosthetic joint infection after hip replacement was required in 0.55% of patients at 1 year,[30] 0.54% at 5 years[31] and 0.62% at 10 years.[32] In a single-centre UK retrospective cohort, 0.45% of patients required revision for infection at 5- to 8-year review.[12]

Knee prosthetic joint infection

In Finnish registry and Republic of Korea national surveillance data, neither of which had methodological concerns, rates of infection after knee replacement were 1.14% at 2 years[27] and 1.9% at 1 year,[26] respectively. In prospective single-centre Finnish and UK cohorts, the infection rates were 0.8% at 1 year[33] and 0.86% at up to 15 years, respectively.[29] In a prospective single-centre Spanish cohort, the incidence of surgical site infection was 1.0% at 90 days.[34] Retrospective single-centre cohorts from the UK and Germany reported infection rates of 0.97% at a mean of 6.5 years[11] and 3.08% at 1 year, respectively.[35]

Revision for knee prosthetic joint infection

The rate of revision for treatment of knee prosthetic joint infection in a UK registry with no methodological concerns was 0.75% at 10 years.[36] In a retrospective single-centre cohort from Taiwan (Province of China), the rate of infection requiring surgical intervention was 1.19% at 2 years.[37]

Treatment options

Patients with prosthetic joint infection and the surgical team face a difficult and protracted course of treatment and recovery. Multiple surgical procedures are frequently required to clear infection and reduce the need for joint excision or amputation. Treatment options include long-term suppressive antibiotic treatment, generally reserved for patients unsuitable for surgery because of comorbidities;[38] debridement, antibiotics and implant retention (DAIR); revision with a single- or two-stage procedure; and temporary replacement with a functional articulating spacer.

Debridement, antibiotics and implant retention

Debridement, antibiotics and implant retention involving extensive debridement and prosthesis retention, but with replacement of modular components such as polyethylene liners, is a treatment option in early post-surgical and late acute infections.[39] DAIR is practical only if there is no evidence of prosthesis loosening or significant damage to soft tissue, and in infections that can be treated with antibiotics.[18] The need for long-term and possibly lifelong antibiotic treatment is acknowledged,[40] and about 55% of patients treated with DAIR may subsequently need implant replacement.[41]

Two-stage revision

Surgical revision involves prosthesis removal, debridement, antibiotic treatment and replacement. In the well-established two-stage procedure, the replacement of the prosthesis is delayed for a period of a few weeks to many months permitting localised antimicrobial strategies and monitoring of infection. However, mobility and quality of life are poor between surgeries. To reduce long-term problems resulting from an extended period without an implant, an antibiotic-impregnated cement 'spacer' may be used to maintain some function and a correct leg length, and to reduce long-term problems associated with non-use. Although spacers improve patient mobility, complications can arise, including spacer dislocations and fractures, and femoral fractures.[42,43]

Single-stage revision

An alternative revision strategy with implant removal, debridement and replacement in one operation has been favoured in some centres[44,45] and is increasingly used in the UK. Although single-stage revision surgery is considered by some surgeons to be appropriate for only a minority of patients, at the Hamburg ENDO-Klinik it has been used in the treatment of 85% of cases of hip prosthetic joint infection.[44]

Functional articulating spacer

Some people who receive the first stage of a two-stage revision for hip prosthetic joint infection and have an articulating spacer fitted achieve a satisfactory outcome and prefer to keep this in place and not undergo the second-stage surgery. Systems have been refined with the aim of providing a potentially long-lasting functional joint with the need for only one operation but, if required, a straightforward second-stage total hip replacement. A custom-made articulating spacer (CUMARS) widely used in the UK has all-polyethylene acetabular components and the Exeter Universal stem (Stryker Orthopaedics, Mahwah, NJ, USA).[46] The stem is fixed in place with antibiotic loaded acrylic cement using a technique that allows for possible removal should a second-stage procedure be required.

Programme development

To support our programme application, we conducted a systematic review comparing single- and two-stage revision procedures in patients with hip prosthetic joint infection.[47] We found 2-year rates of reinfection or development of a new infection after single-stage revision of 8.6% [95% confidence interval (CI) 4.5% to 13.9%] and after two-stage revision of 10.2% (95% CI 7.7% to 12.9%). We limited bias by including series of consecutive patients with hip prosthetic joint infection treated exclusively by single- or two-stage revision. We concluded that randomised trials were needed to establish optimum management strategies. Furthermore, the evidence base was highly limited regarding health service, patient and economic significance, risk factors, patient and surgeon experiences, diagnosis, and patient preferences for treatments.

Programme development: patient and public involvement

Collaboration with patient-partners took place through meetings with our dedicated patient and public involvement (PPI) group, the Patient Experience Partnership in Research (PEP-R), which comprised nine people who had musculoskeletal conditions.[48] The group met every 6–8 weeks, providing input into project design and conduct. Through ongoing training and support from research staff and our patient involvement co-ordinator, group members were familiar with research designs, conduct and some of the barriers to successful research. We used National Institute for Health and Care Research (NIHR) INVOLVE guidance to ensure that PPI was appropriately organised[49] and we were part of the South West 'People in Research' consortium.

In December 2010, February 2011 and September 2011 we discussed the planned research with PEP-R. The group believed that, although relatively few people developed an infection, the research was important. They noted the need for feasibility work to assess the acceptability of randomisation. They offered their full support for future work and we considered their ongoing involvement crucial to ensure that the project reflected the priorities of the public and was interwoven throughout the programme.

The INFORM programme

The overall aim of the INFORM (INFection ORthopaedic Management) programme was to identify methods that may improve treatments and outcomes for patients with deep prosthetic joint infection

after total hip or knee replacement. Studies were grouped by research methodology into seven work packages, all supported by PPI (*Figure 1*):

- Work package 1. We aimed to conduct systematic literature reviews of treatments for prosthetic joint infection after hip and knee replacement and conduct an individual patient data (IPD) meta-analysis to compare reinfection outcomes after single- and two-stage revision surgery. We also aimed to review risk factors, methods of diagnosis and costs.
- Work package 2. We aimed to analyse the National Joint Registry for England, Wales, Northern Ireland and the Isle of Man (NJR) to identify the predictors of prosthetic joint infection after hip and knee replacement and to compare outcomes according to health-care characteristics.
- Work package 3. Through qualitative interviews, we aimed to assess the impact on patients of prosthetic joint infection and treatment strategies, surgeons' views on treatment, and patients' and surgeons' views on a randomised trial.
- Work package 4. In a randomised controlled trial (RCT) with embedded qualitative interviews, we aimed to investigate whether or not treating hip prosthetic joint infection 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 we aimed to assess the economic implications of prosthetic joint infection and treatment strategies. We also aimed to conduct a comprehensive economic evaluation within the RCT comparing single- and two-stage revision for treatment of hip prosthetic joint infection.
- Work package 6. Through a discrete choice questionnaire, we aimed to assess the trade-offs that patients are willing to make between patient-reported and clinical outcomes and explore the degree to which treatment strategies change preferences for those outcomes.
- Work package 7. Finally, we aimed to disseminate findings to patients, the public, clinicians and stakeholders.

Work packages were conducted in parallel. An exception was the work package 3 qualitative study looking at surgeon decision-making, which directly influenced the design of the INFORM RCT in work package 4. The study of patient preferences in work package 6 followed on from the INFORM trial but focused on patient experiences of surgical treatments independently of trial participation.

Changes to the programme and additional research

Planned research is published, has been submitted to a journal or is being written up. We have also received a NIHR Programme Development Grant to develop recommendations based on the INFORM findings and explore implementation.

An additional published systematic review of outcomes after DAIR is summarised. Further studies included systematic reviews of risk prediction tools, health-care needs and support, and treatment comparisons in ankle and shoulder infection; and a UK survey of care pathways.

We had originally planned to examine the accuracy, costs and cost-effectiveness of a broad range of methods for diagnosing and monitoring infection. Ultimately, in the programme, we focused on new promising biomarkers for the diagnosis of infection.

In NJR analyses, we planned to compare outcomes in 'specialist' and other centres. We were unable to define 'specialist' centre and have compared care according to different health-care characteristics.

The NJR and Hospital Episode Statistics (HES) linked analysis of economic burden of hip prosthetic joint infection was completed as planned. The study of knee prosthetic joint infection has been delayed as the COVID-19 pandemic prevented on-site access to NJR data.
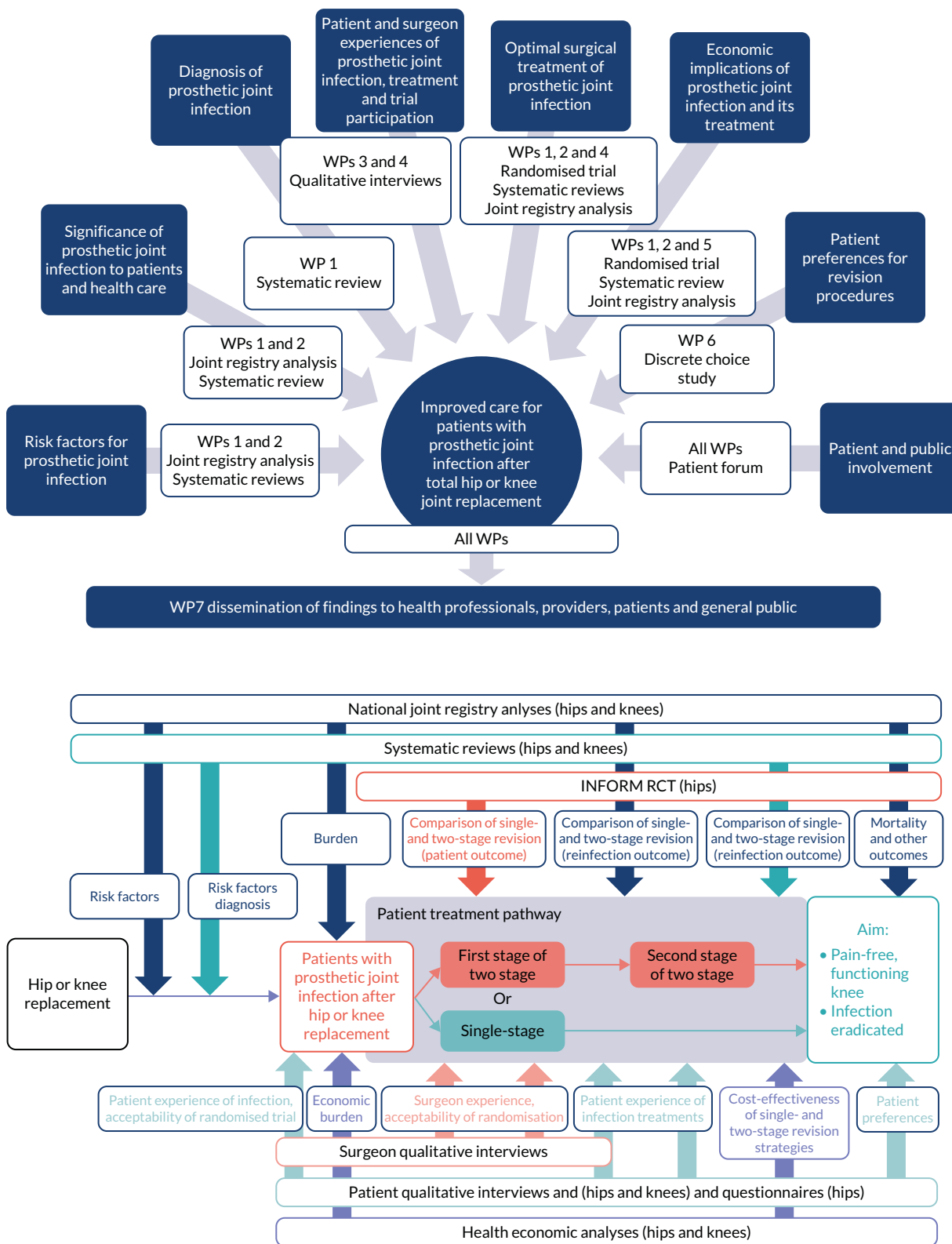
FIGURE 1 The INFORM programme. WP, work package.

INFORM: organisation and management

The INFORM programme was run and co-ordinated by the Musculoskeletal Research Unit at the University of Bristol and North Bristol NHS Trust.

Programme Steering Committee

The programme was overseen by a Programme Steering Committee chaired by Professor Rod Taylor, NIHR Senior Investigator and Professor of Health Services Research, University of Exeter. Other independent committee members were Martyn Porter, the past president of the British Orthopaedic Association and Medical Director of the NJR; Ali Heawood, Senior Research Fellow in Qualitative Primary Care Research; and Julie Chappell, a solicitor specialising in medico-legal negligence. The Programme Steering Committee met on nine occasions (every 6 months), with at least three independent members present, to monitor the progress of the programme and help the research team to meet agreed milestones. They expressed their satisfaction with progress in all work packages but noted the slow recruitment to the RCT and supported measures to enhance recruitment, in particular the inclusion of more sites.

Pan-programme group

The pan-programme group (research team, co-applicants, site principal investigators and sponsor representative) met on 24 occasions (every 3 months) to discuss progress, outputs and dissemination from each of the work packages.

Work packages

Each work package lead arranged an internal working group that met regularly to ensure the delivery of agreed outputs. Work package 4 was run by the Trial Management Group (chief investigator, site principal investigators, co-applicants, trial manager, statistician, health economist, qualitative researcher and methodologist from Bristol Randomised Trials Collaboration), which met monthly to design and deliver the randomised trial.

Data monitoring committee

For work package 4, an independent data monitoring committee was established, consisting of a trial methodologist and two orthopaedic surgeons. This committee met on four occasions and reported directly to the Programme Steering Committee.

Microbiology

A meeting was held in 2014 with the lead consultant clinical microbiologists from four of the trial sites (Bristol, Exeter, Oxford and Cardiff). The group assisted with trial design and participant recruitment processes and advised on the collection of microbiological, antibiotic and blood biomarker data.

Study sponsor

Good Clinical Practice, local research governance and finance were overseen by the study sponsor (North Bristol NHS Trust Research and Innovation Department) and the University of Bristol. NHS Research Ethics and Research and Development approvals were obtained for work packages 3, 4 and 6.

INFORM randomised controlled trial

Selection of centres
Four centres were specified in the application and surgeons from each centre were co-applicants. To address early low recruitment rates, more sites were added. Eligible sites were high-volume tertiary referral centres for infected joint replacements, or large NHS orthopaedic units. Participating surgeons had experience of and expertise in both single- and two-stage revision treatment for hip prosthetic joint infection. Surgeons from Sweden showed interest in the research and Swedish centres joined the trial in 2016.

Training of researchers
We held workshops with recruiting nurses to provide training and support for the identification and recruitment of patients. Audio-recordings of recruitment interviews were used to explore, critique and improve the role of research nurses in the recruitment process. Recruiters met on three occasions and held monthly teleconferences with the trial manager to discuss recruitment and share their experiences of recruitment interviews.

Publication committee

To achieve high publication standards, an INFORM publication policy was adhered to. Manuscripts and conference articles were approved by the committee prior to submission. The committee consisted of Professor Ashley Blom (chief investigator), Professor Rachael Gooberman-Hill (qualitative lead) and Mr Stephen Jones (orthopaedic surgeon).

Patient and public involvement in the INFORM programme

Aims

The aims of our PPI were to gain input into the design of patient recruitment and information literature, research processes and questionnaires; identification of outcomes of importance to patients; and dissemination strategies. PPI also helped to ensure that milestones were met and that input was provided into the interpretation of data and findings:

> *It feels that between us all we may make a difference to patients who may have an infection.*
>
> *INFORM forum group member*

Patient and public involvement

Patients have been crucial to the success of this research in the following ways:

The Patient Experience Partnership group
The PEP-R group is the dedicated patient involvement forum at the Musculoskeletal Research Unit, University of Bristol, which comprises nine people who have musculoskeletal conditions, most of whom have had joint replacement.

INFORM patient forum
To complement the PEP-R group's activities, it had been proposed that each work package would have an oversight forum including patient-partners who had experience of infection following joint replacement. When talking to patients, it became apparent that they wanted to be involved in work package oversight through a forum that met regularly. Four patients agreed to take part and the first meeting was held in December 2013. An additional patient was keen to be involved but was house-bound while waiting for revision surgery. This patient joined the forum in April 2015:

> *It has been fantastic to have a group of patients with this rare condition who are happy to meet and discuss the project at regular intervals.*
>
> *INFORM researcher*

Arthritis Care/Versus Arthritis
In the development of the programme, we collaborated with Arthritis Care. It had been proposed that a representative from Arthritis Care would sit on the programme's steering committee. Following a change in organisation within the charity, this was no longer possible. We plan to work with Versus Arthritis in disseminating details of the study to their members, their volunteers and the wider public.

Steering committee
A lay partner was a member of the Programme Steering Committee. This group received regular reports on the PPI activity.

Patient and public involvement meetings

Members of the PEP-R group worked on the grant application and were involved throughout the programme. A meeting in March 2020 to share results was postponed due to the COVID-19 pandemic. We will continue working with the group remotely. PEP-R group members helped to prepare the *Plain English summary* for this report.

The INFORM patient forum has met 33 times and provided input into all work packages. We are continuing to work with the forum remotely to complete work on writing an information leaflet for newly diagnosed patients, reviewing information on prosthetic joint infection on the internet, writing a summary of results for trial participants, creating infographics, finishing their conference presentation, and working with Versus Arthritis to support and inform patients who have prosthetic joint infection. The PPI activity is summarised in *Table 1*.

TABLE 1 The INFORM PPI activity

Type	PPI activity and actions	Date of PPI activity
WP1		
INFORM	Discussed findings and public dissemination	April 2016, February 2017
WP2		
INFORM	Discussed NJR	June 2014
INFORM	Discussed the predictors of prosthetic joint infection	February 2016
INFORM	Discussed *The Lancet* hip paper[50] and public dissemination	June 2018
INFORM	Reviewed *The Lancet* hip paper[50] press release	September 2018
INFORM	Discussed *The Lancet* knee paper[51]	September 2018
WP3		
INFORM	Discussed the design of the interview study and important interview questions	February 2014, April 2014
INFORM	Discussed study summaries of findings for participants	August 2015
INFORM	Discussed the findings from interviews with hip patients and the plans to interview knee patients	February 2016
INFORM	Discussed a peer-support programme for patients having treatment for infection or other complication following joint replacement	November 2017
INFORM	Discussed the findings of the interviews with surgeons	April 2018
INFORM	Discussed the findings of the interviews with patients	April 2018, June 2018
INFORM	Discussed peer-support programme for patients having treatment for infection or other complication following joint replacement	June 2018
INFORM	Discussed the findings on information needs from the interviews with hip and knee patients	April 2019
INFORM	Discussed public dissemination	April 2018, June 2018, September 2019, November 2019
WP4		
INFORM	Discussed the design of the trial, the patient information leaflet, recruitment information and questionnaires	April 2014, September 2014, November 2014
PEP-R	Reviewed patient information leaflet and questionnaires	September 2014
INFORM	Discussed feedback and information for trial clinicians and researchers	June 2015
INFORM	Discussed patient recruitment strategies	April 2016, January 2018
INFORM	Discussed the extension to the trial	June 2017
INFORM	Discussed a feasibility study of revision surgery for knee infections	October 2017
INFORM	Discussed the design of an update leaflet for trial participants	February 2018, April 2018
PEP-R	Discussed results and public dissemination	September 2019

TABLE 1 The INFORM PPI activity (*continued*)

Type	PPI activity and actions	Date of PPI activity
WP5		
INFORM	Discussed the resource use diaries and questionnaires	June 2014, November 2014
WP6		
INFORM	Discussed the discrete choice questionnaire	February 2015, April 2015, September 2016, November 2016
INFORM	Discussed the results	July 2019
WP7		
INFORM	Discussed that findings should be written up as a patient information booklet in printed and electronic versions and short films	February 2015, November 2016, November 2018, February 2019, September 2018, ongoing
INFORM	Reviewed the film on the evaluation of the INFORM PPI group	September 2018
INFORM	Discussed public dissemination of the trial	July 2019
INFORM	Discussed the published papers to date	April 2019
INFORM	Discussed important things to tell surgeons about PPI	September 2019
INFORM	Discussed their conference presentation	January 2020, ongoing
INFORM	Discussed the conference invitations, timings, speakers, venue and agenda	September 2019, January 2020, ongoing
PEP-R	Discussed the conference	September 2019
INFORM	Discussed the summary leaflet for participants/infographics	Ongoing
Final report		
PEP-R	Read and revised draft versions of the final report *Plain English summary*	May 2020

WP, work package.

Contributions to INFORM and impact on programme

The impact of the INFORM patient forum on programme conduct and dissemination is summarised in *Tables 2* and *3*. In *Box 1* we summarise INFORM researcher comments on PPI impact as reported in evaluations in 2014 and 2019.

Public dissemination

Dissemination of the results from INFORM is ongoing. A 1-day conference to share results with study participants, patient-partners, carers and the general public was planned for May 2020 but has been delayed because of the COVID pandemic.

Our film about the INFORM randomised trial was featured on University of Bristol and NIHR websites in June 2018. By 22 February 2020 it had been viewed 378 times (www.youtube.com/watch?v=_ AH1Nu3tWVch).

TABLE 2 The INFORM PPI forum impact on programme conduct

What they told us	Impact
We should 'take the research to the patient' rather than 'take the patient to the research'	We established a new patient forum for the programme, and the researchers came to them to discuss all the WPs, rather than patients sitting on steering groups
This was the first time they had spoken to other patients who had experience of infection following joint replacement: *When infection is diagnosed you feel as though it doesn't happen to anyone else. Interesting to hear others' experiences* *INFORM PPI group member*	Social time was built in to meetings
Infection following joint replacement has a considerable impact on their families as well as them	The forum members felt that relatives and significant others should also be involved with the forum and it was decided that they should be invited to attend selected meetings. Two relatives joined the meeting in September 2014 at which we discussed the trial and the patient recruitment information The forum members suggested that 2020 conference attendees could invite someone to come with them
PPI needs to support patients with mobility issues	One forum member could attend by taxi only and there were times when others were unwell and unable to drive. We were fortunate that we had applied for funding to offer taxis to forum members
They wanted to know about the other PPI work and research being carried out by our unit	The forum members visited the Musculoskeletal Research Unit offices and had several opportunities to meet researchers outside the forum. In January 2015 we held an event so that the PEP-R forum members and the INFORM forum members could meet. Both groups enjoyed finding out about each other's work and will have the opportunity to meet up at a planned INFORM conference when the COVID-19 pandemic allows
Forum members wanted to know about their impact on the programme: *From your comments I feel sure that the group has helped you in your research* *INFORM PPI group member*	Forum members received verbal updates and feedback leaflets on previous meetings, including changes made by researchers following discussions with the group
Forum members were very positive about the PPI: *I'd just like to say it's been one of the most interesting things I've ever been involved in* *INFORM PPI group member*	In 2014, forum members and researchers were given a questionnaire evaluating the group. In 2020, the forum members took part in an evaluation of the PPI work within the unit. The findings are being written up for publication

WP, work package.

Our film about the PPI evaluation was tweeted about by the University of Bristol and featured in the INVOLVE September 2018 newsletter. By 22 February 2021 it had been viewed 231 times (www.youtube.com/watch?v=TrZfHfVaMZE).

The Musculoskeletal Research Unit website is at www.bristol.ac.uk/translational-health-sciences/research/musculoskeletal/orthopaedic/research/inform.html and INFORM Twitter (Twitter, Inc., San Francisco, CA, USA; www.twitter.com) account is at https://twitter.com/BristolINFORM.

TABLE 3 The INFORM PPI forum impact on programme dissemination

What they told us	Impact
All five members remain committed and enthusiastic members of the research team: *I've just thoroughly enjoyed it; it gave me my confidence back again* *INFORM PPI group member*	All forum members are keen to share their experiences of being involved in the patient forum and one member will speak on behalf of the group at the 2020 conference
They identified that there is a lack of support services for patients with infection following joint replacement: *I've benefited from meeting other people in a similar situation to me* *INFORM PPI group member*	Based on this we developed a new grant application; unfortunately, this was unsuccessful. We are now working with Versus Arthritis to see if it can be a signpost for patients to find existing support services
They identified the lack of patient information on infection following joint replacement. They suggested that a website or booklet with information would be insightful	We are working together to write up the findings as a patient information booklet to be given out in infection clinics. We plan to share this information with Versus Arthritis to update its website
They identified the importance of keeping participants informed when the trial was extended	We took their advice and sent update leaflets to participants to keep them engaged with the trial
They told us that the conference should be in plain English	We have taken their advice on conference invitations, timings, speakers, venue, inviting participants' family members to attend and agenda. Twenty-five participants and their partners registered to attend the conference in May 2020

BOX 1 The INFORM researcher comments on the impact of PPI on the programme

> *PPI was essential in the grant application . . . the views of patients were essential in development of diverse work packages . . . helped to shape the way I think about different methods used to treat infected joint replacement . . . the different responses and questions from patients compared with researchers and clinicians at scientific meetings.*
>
> *Their advice greatly improved the patient information sheets and the planned ways of approaching and discussing the trial with potential participant.*
>
> *The success of our ethics application is a reflection of the PPI work.*
>
> *They valued the research and answered questions only they could answer. If you want to understand whether your research will work and if it is of value from a patient's perspective, then ask a patient! It also helped me to very quickly gain an insight into the impact of the condition, giving me a head start, orientating me, and sharpening my focus in order to further develop our approach and design.*
>
> *Having been through treatment themselves they were able to provide us information on home care and home changes that we had not previously known. This allowed us to amend and improve these sections (of the health economics questionnaires).*

The significance of prosthetic joint infection to health care

Here we summarise our published NJR analyses,[32,36,52] and an unpublished review is given in *Appendix 2*.

Aims

We aimed to describe the risk of revision due to prosthetic joint infection for patients undergoing primary and revision hip or knee replacement, the changes in risk over time and the overall significance of prosthetic joint infection to the NHS. Supported by a systematic review, we aimed to estimate the economic significance of revision for hip prosthetic joint infection.

Methods

Surgeon, patient and health-care implications of hip and knee prosthetic joint infection

We analysed revision surgeries performed as a result of a diagnosis of prosthetic joint infection linked to index procedures recorded in the NJR between 2003 and 2014.[8] Revision surgeries were a single stage or the first stage of a two-stage revision, hip excision or a DAIR procedure with modular exchange.

Prevalence, cumulative incidence functions and the burden of all procedures for the treatment of prosthetic joint infection were calculated. To investigate time trends in the risk of revision for hip and knee prosthetic joint infection, we plotted the time from index surgery (primary or aseptic revision) to revision for infection and compared rates within 3 months, between 3 and 6 months, 6 months to 1 year, 1–2 years, 2–3 years, 3–4 years and 5–6 years. Log-linear regression, using the year of the index knee replacement as a continuous independent factor, was used to explore overall linear trends between 2005 and 2013.

Health economic consequences of prosthetic joint infection treatment: systematic review

The protocol was registered on PROSPERO (CRD42017069526). We searched MEDLINE and EMBASE on Ovid from inception to 10 April 2019 with no language restrictions. Studies included in our other systematic reviews were inspected. Inclusion criteria were:

- patients with hip or knee prosthetic joint infection after primary replacement or aseptic revision
- intervention relating to revision surgery
- comparator with no prosthetic joint infection or alternative surgical treatment
- outcome of cost-effectiveness or comparative costs
- full economic evaluation or cost comparison study.

After detailed screening by two reviewers, data were extracted on study setting, patient characteristics, treatments, dates, sources of cost information, currency, costs and issues relating to quality assessment.

Health economic consequences of prosthetic joint infection: NJR analysis

Patients with hip prosthetic joint infection who received a single- or two-stage revision procedure in England between 2006 and 2009 were matched 1 : 5 with patients who had neither infection nor revision. Matching was based on age, sex, American Society of Anesthesiologists (ASA) grade, total or resurfacing hip replacement, date of primary surgery and hospital. If fewer than five patients could be matched adequately with cases, then available patients with no infection were included.

Using patient health-care records from English Hospital Episode Statistics (HES) and values from 2014/15 UK national reference costs, overall hospital inpatient and day-case costs were calculated for the first 5 years after primary hip replacement. Costs were not limited to orthopaedic health care. Incremental differences in costs between those revised and those not revised for prosthetic joint infection were estimated using a two-part model (probit and generalised linear model).

Results

Surgeon, patient and health-care implications of hip prosthetic joint infection

The NJR cohort analysis included 623,253 primary hip replacements and 63,222 aseptic revision hip replacements. A total of 7040 patients required one or more courses of revision surgery to treat prosthetic joint infection ($n = 7585$ procedures). Of these, 3338 patients ($n = 3546$ procedures) had no first surgery recorded in the NJR. Thus, our analyses were limited to 3702 patients ($n = 4039$ procedures), of whom 2705 had an index primary hip replacement ($n = 2926$ procedures) and 997 had a revision hip replacement ($n = 1113$ procedures).

The cumulative incidence functions of revision for prosthetic joint infection following index primary and aseptic revision hip replacement are shown in *Figure 2*. The probability of revision for prosthetic joint infection after a primary hip replacement was 0.15% (95% CI 0.14% to 0.16%) at 1 year and 0.62% (95% CI 0.59% to 0.65%) at 10 years. The probability of revision for prosthetic joint infection following an aseptic revision was higher, with rates of 0.69% (95% CI 0.63% to 0.76%) at 1 year and 2.25% (95% CI 2.08% to 2.43%) at 10 years.

The prevalence of revision due to prosthetic joint infection in the 3 months following primary hip replacement more than doubled between 2005 and 2013 (rate ratio 2.29, 95% CI 1.28 to 4.08; time trend likelihood ratio test $p < 0.0001$). No time trends for revision for the time periods 3–6 months, 6 months to 1 year and 1–2 years were found. However, later rates of revision prosthetic joint infection decreased over time (between 2 and 3 years rate ratio 0.52, 95% CI 0.32 to 0.84, time trend $p < 0.0001$; between 3 and 4 years rate ratio 0.49, 95% CI 0.31 to 0.80, time trend $p = 0.001$; and between 4 and 5 years rate ratio 0.44, 95% CI 0.27 to 0.73, time trend $p = 0.028$).
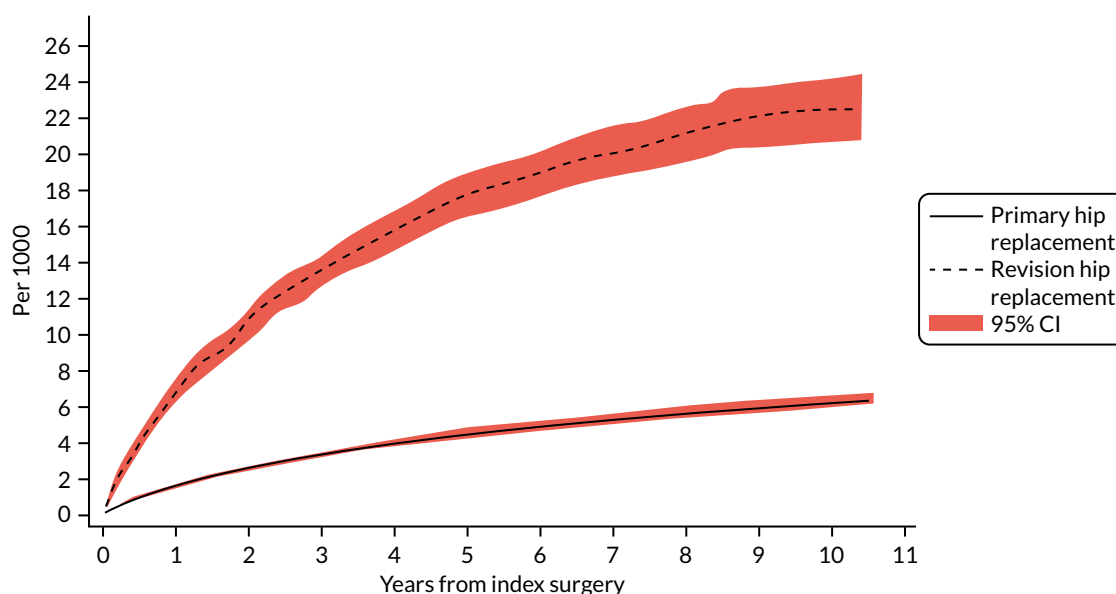
FIGURE 2 Cumulative incidence function of revision for prosthetic joint infection following index primary and aseptic revision hip replacement.

The absolute number of procedures performed annually to treat infection increased from 384 in 2005 to 1002 in 2014, a 2.6-fold increase. This was greater than the twofold increase in primary procedures during this period.

Overall, 70% of revisions for prosthetic joint infection after hip replacement were two-stage procedures. However, in 2014, 60.7% of revision surgeries were carried out with a two-stage procedure and 29.7% were carried out with a single-stage procedure. The use of DAIR rose from < 1% of revision surgeries in 2005 to 7.6% in 2014.

Surgeon, patient and health-care implications of knee prosthetic joint infection

Between 2003 and 2014, 679,010 index primary knee replacements and 33,920 index revision knee replacements were registered in the NJR. A total of 8247 revision total knee replacements were performed as a result of a diagnosis of prosthetic joint infection. Our analyses of prevalence were limited to 3659 patients with a primary knee replacement (4004 procedures) and 717 patients with a revision knee replacement (785 procedures) as 3458 index operations had been conducted before the establishment of the NJR.

The cumulative incidence functions of revision for prosthetic joint infection following index primary and aseptic revision knee replacement are shown in *Figure 3*. The probability of revision knee replacement due to prosthetic joint infection was 0.17% (95% CI 0.16% to 0.18%) at 1 year and 0.75% (95% CI 0.72% to 0.78%) at 10 years. The probability of revision for prosthetic joint infection following an aseptic revision was higher, with rates of 0.76% (95% CI 0.68% to 0.86%) at 1 year and 3.13% (95% CI 2.81% to 3.49%) at 10 years.

Revision rates within 3 months of the index knee replacement increased over time, with the prevalence rate in 2013 over twice that in 2005 (rate ratio 2.46, 95% CI 1.15 to 5.25; $p < 0.0001$). No time trends for revision for other time periods were apparent with the exception 5–6 years, which decreased over time (rate ratio 0.53, 95% CI 0.33 to 0.86; time trend $p = 0.018$).

In 2014, 1048 revision procedures were performed to treat knee prosthetic joint infection compared with 378 in 2005, a 2.8-fold increase. Overall, 75% of revision operations were conducted as a two-stage procedure, but there was an increase in use of single-stage revision from 7.9% in 2005 to 18.8% in 2014. The use of DAIR also increased, from 2.1% in 2005 to 9.1% in 2014.
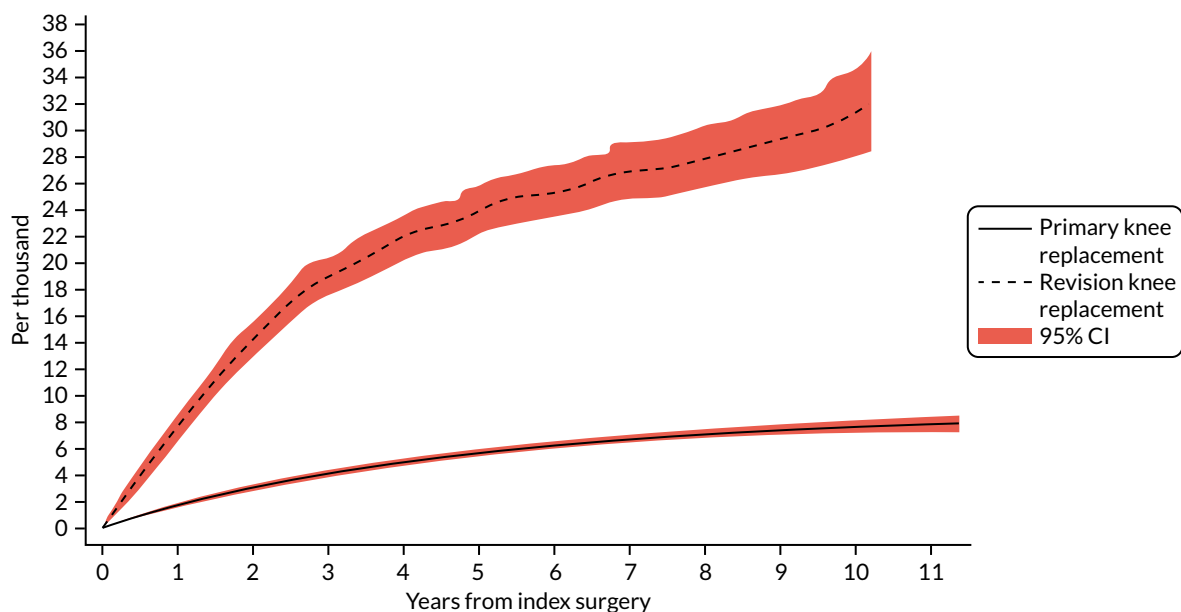
FIGURE 3 Cumulative incidence function of revision for prosthetic joint infection following index primary and aseptic revision knee replacement.

Health economic consequences of prosthetic joint infection: systematic review

As shown in the flow diagram in *Appendix 2, Figure 17*, after detailed evaluation of 228 potentially relevant articles, 19 studies were included in the review, of which two were conducted in the UK. Fifteen studies reported cost comparisons of revision procedures for prosthetic joint infection with primary joint replacement or aseptic revision. Three studies presented cost comparisons between single-stage and two-stage revision procedures. In two studies, costs associated with different spacers were compared.

Cost of prosthetic joint infection treatment compared with primary hip or knee replacement

Eight studies reported comparisons between primary hip or knee replacement and first surgical treatments of infected hip or knee replacements other than DAIR. Treatments for infection cost on average 4.0 times (range 2.9–5.3 times) that of primary hip or knee replacement. DAIR treatment cost on average 3.0 times (range 2.9–3.1 times) that of primary hip or knee replacement. In one study that included costs of primary hip or knee replacement and subsequent first treatments for infection, including those occurring during primary admission, the costs were 2.9 times that of primary hip or knee replacement.

Only the cost of the first treatment for hip infection was measured in one study, and this was 3.6 times the cost of primary hip replacement.

In four studies the cost of revision for infection and any subsequent treatments relating to infection were calculated. On average, revision for infection treatment and further treatments cost 4.5 times (range 3.7–5.3 times) that of primary hip or knee replacement.

In two studies including costs of primary hip or knee replacement and all subsequent treatments for infection including persistent infection and reinfection, the costs reported were 3.5 and 4.1 times that of primary hip or knee replacement, respectively.

Cost of infection treatment compared with cost of aseptic revision

In seven studies, the average cost of revision for infection was 2.4 times (range 1.5–3.1 times) that for aseptic reasons and this was similar in the five studies exclusively reporting two-stage revision. In five studies, the cost of revision surgery was reported with no consideration of subsequent reoperations for failure of infection clearance. In these studies, the cost associated with treatment of infection was 2.3 times (range 1.5–3.1 times) that of aseptic revision. In five studies in patients with hip replacements, costs of revision for infection were 2.4 times those of aseptic revision (range 1.8–2.8 times). This difference was 3.1 and 1.5 in the two studies in patients with knee replacement. In two UK studies, the hospital costs of two-stage treatment of hip infection were 1.8 times greater, and for knee infection 3.1 times greater, than aseptic revision.

Costs of single-stage compared with cost of two-stage revision strategies

In two studies the cost of planned revision with no further treatment for persistent infection or reinfection using a two-stage procedure was higher than for a single-stage procedure, with a two-stage revision costing 1.7 times or 1.6 times that of a single-stage revision.

Considering all procedures, including planned operations and those required to treat persistent infection or reinfection, the relative costs differed in two studies reporting data. In one study, 3 out of 25 patients required additional treatment after single-stage revision and 1 out of 14 required this after two-stage revision. Considering the additional costs associated with these procedures, the overall cost of treatment with two-stage revision was about 1.6 times that of single-stage revision. In another study, five out of six single-stage revisions required additional operations and the overall cost of a two-stage revision was 0.6 times that of a single-stage revision.

Health economic consequences of hip prosthetic joint infection: NJR analyses

A total of 609 patients who had first revision surgery for hip prosthetic joint infection and whose primary operation had been recorded in the NJR between 2006 and 2009 met the inclusion criteria. Of these, 422 could be linked to HES for required variables and matched to a comparator patient with no revision surgery for hip prosthetic joint infection. Healthcare Resource Groups (HRGs) were available for 98% of hospital admissions, and weighted average costs of adult HRGs by admission type were applied to those remaining.

Our analysis included 422 patients with prosthetic joint infection after hip replacement and 1923 matched patients with no infection. Patients revised for hip prosthetic joint infection had an average of eight admissions during the 5 years after primary hip replacement compared with three admissions in those with no infection. Of the patients with no infection, 76% had an inpatient or day-case admission. In the 5 years following primary hip replacement, the average cost of inpatient and day-case admissions was £41,633 (95% CI £39,079 to £44,187) for patients with prosthetic joint infection and £8181 (95% CI £7614 to £8748) for those with no infection, a difference in costs of £33,452 (95% CI £30,828 to £36,077) (*Table 4*). The difference in costs between the groups decreased each year during the 5 years following primary hip replacement but was still nearly £3000 (95% CI £1999 to £3720) by the fifth year.

Conclusions

The 10-year rates of revision for prosthetic joint infection after hip and knee replacement were 0.62% and 0.75%, which are lower than those in Scandinavian registries.[30,31] People receiving aseptic revision were at four times greater risk of hip or knee prosthetic joint infection.

There was a suggestion that prosthetic joint infection rates rose between 2005 and 2013. This was limited to the first 3 months after primary surgery and may reflect earlier identification and treatment of infection. The use of single-stage revision and DAIR has increased, and although the use of two-stage revision has decreased it is still the most widely used treatment.

Registry analyses showed fivefold higher health-care costs in the 5 years after primary surgery for people with prosthetic joint infection than for people with no infection. This was consistent with studies from Canada, France, Germany and the USA that reported costs of revision for infection and subsequent treatments ranging from 3.7 to 5.3 times that of primary hip or knee replacement. Comparative costs of treatment strategies are dependent on the success rate of treatments, which varied markedly in studies comparing single- and two-stage revision.

TABLE 4 Average total and annual inpatient and day-case hospital admission costs over the 5 years following hip replacement in patients with hip prosthetic joint infection and those with no infection

	Cases (n = 422), adjusted cost (£), mean (SE)	Controls (n = 1923), adjusted cost (£), mean (SE)	Adjusted difference in costs (£) (95% CI)
First year post primary	14,686 (816)	1959 (111)	12,727 (11,094 to 14,360)
Second year post primary	10,575 (682)	1503 (91)	9071 (7719 to 10,424)
Third year post primary	6974 (580)	1512 (97)	5462 (4306 to 6618)
Fourth year post primary	5168 (501)	1584 (131)	3584 (2611 to 4557)
Fifth year post primary	4427 (431)	1568 (101)	2859 (1999 to 3720)
Total over 5 years	41,633 (1303)	8181 (289)	33,452 (30,828 to 36,077)

SE, standard error.
Two-part model (probit and generalised linear model) adjusted for age, sex, ASA grade, diagnosis of osteoarthritis, operation date, Charlson Comorbidity Index, bearing surface and procedure.

Limitations

In NJR analyses, we do not know how many people had an infection that was not treated surgically. However, the number treated without surgery is probably small as biofilm involvement means that antibiotic treatment alone can only suppress infection. Furthermore, arthroscopic management is not recommended.[53] In a Swedish cohort, 91% of people treated for prosthetic joint infection, and who subsequently received continuous outpatient antibiotic treatment, underwent a reoperation.[28] The UK Bone and Joint Infection Registry (BAJIR), established in 2018, collects information on all patients diagnosed with prosthetic joint infection in the UK and will provide accurate estimations of infection rates.[54]

In the systematic review, the resources included in cost calculations varied considerably. In a comparison of costs and cost-effectiveness, future larger-scale and longer-term studies should assess costs to health service providers, social care and society, including those attributable to further treatments and revision operations.

In our NJR analysis, we estimated the burden of hip prosthetic joint infection with respect to inpatient and day-case admissions but did not consider costs relating to outpatient, primary and community care, and prescribed medications. Including these would have increased the overall costs in both patients who were and patients who were not treated for hip prosthetic joint infection and would probably have increased the cost difference between the two groups. For patients revised for hip prosthetic joint infection, the average cost of inpatient and day-case admissions in the 5 years following primary total hip replacement (including the cost of revision for prosthetic joint infection) was £41,633 using 2014–15 costs. Vanhegan *et al.*[55] reported that the cost of revision for hip prosthetic joint infection alone was £21,937 at a single UK hospital using costs from 2007–8. The authors found that this cost did not reflect NHS tariffs, which were considerably lower. Assuming that this underestimate is true and also holds for NHS reference costs (which were used in this study), the financial burden of hip prosthetic joint infection may have been underestimated.

As HES include hospital admissions at NHS hospitals in England only, the cost of admissions funded by the NHS outside England or in private facilities was not included. An estimated 83% of hip revision procedures are conducted in NHS hospitals.[56] With the need for involvement of an arthroplasty surgeon experienced in treating prosthetic joint infection and a well-co-ordinated multidisciplinary team, complex cases requiring revision surgery are conducted almost exclusively in NHS orthopaedic centres.

In the INFORM randomised trial, health service, social care and participant resource use data were collected and used in the cost-effectiveness analysis.

Patients' experiences of prosthetic joint infection after hip or knee replacement and its treatment

Here we present an overview of two of our published articles.[57,58]

Aims

We aimed to describe patients' experiences and the impact of revision treatment for prosthetic joint infection after hip and knee replacement, and to compare patients' experiences of single-stage and two-stage revision surgery.

Methods

We conducted qualitative semistructured interviews with patients who had received surgical revision for prosthetic joint infection after hip or knee replacement. Thirty-five patients (19 hip replacement and 16 knee replacement) from five NHS orthopaedic departments in England and Wales were interviewed between 2 weeks and 12 months after they had been discharged from hospital. Interview topic guides were developed in collaboration with the INFORM PPI group. The use of the topic guide was flexible to ensure that key topics were covered but that participants were able to discuss issues they considered important. The questions addressed included those on the experience of prosthetic joint infection, revision surgery and care, the impact of infection and treatment, and thoughts about recovery and the future. We asked participants who had received two-stage revision about their experiences of the time between operations. Data were audio-recorded, transcribed, anonymised and analysed thematically[59] using the qualitative data management software NVivo 10 (QSR International, Warrington, UK).

Results

Prosthetic joint infection after hip replacement

Nineteen patients participated and gave consent. The patient group comprised 12 men and seven women with a mean age of 73 years (range 56–88 years); nine had received a single-stage revision and 10 had received a two-stage revision. Patients reported receiving 1–15 revision operations after their primary hip replacement. Analysis indicated that participants made sense of their experience through reference to three key phases: the period of symptom onset, the treatment period and protracted recovery after treatment. By conceptualising their experience in this way, and through themes that emerged in these periods, they conveyed the ordeal that prosthetic joint infection represented. Patients' revision histories were often complex, extending over many years. Prosthetic joint infection and revision surgery affected all aspects of patients' lives, physically, psychologically, socially and financially. Finally, considering the challenges of prosthetic joint infection, they described the need for support in all phases. Two-stage revision had a greater impact on participants' mobility and resulted in additional complications.

Prosthetic joint infection after knee replacement

Interviews were conducted with 16 patients who consented to the study. The patient group comprised nine men and seven women with a mean age of 72 years (range 59–80 years); nine had received a single-stage and seven had received a two-stage revision. Participant experiences could be characterised

according to three aspects of biographical disruption that we used to frame our analysis: onset and the problem of recognition; emerging disability and the problem of uncertainty; and chronic illness and the mobilisation of resources. Although the experiences of infection and treatment varied, all patients reported the devastating effects of infection and revision treatment. Participants described the use of social and health-care support and a need for more support. Some participants thought that the symptoms with which they had first presented had not been taken seriously enough.

Conclusions

Prosthetic joint infection is life-changing and has an impact on all aspects of a patient's life. Among patients who had undergone revision surgery for prosthetic joint infection, a two-stage procedure had greater impact on participants' well-being than a single-stage procedure because the time between revision procedures meant long periods of immobility, pain and related psychological distress. Participants expressed a need for more psychological and rehabilitative support during treatment and long-term recovery.

Surgeons' decision-making for single-stage and two-stage revision surgery for prosthetic hip joint infection

Here we present an overview of our published article.[60]

Aims

We aimed to explore decision-making by consultant orthopaedic surgeons about the use of single- or two-stage revision surgery for patients with hip prosthetic joint infection to inform our assessment of the feasibility of a randomised trial.

Methods

To guide the development of the INFORM multicentre RCT, we conducted semistructured interviews with 12 consultant surgeons performing revision surgery for hip prosthetic joint infection at five high-volume NHS orthopaedic departments in England and Wales. We analysed the data thematically.

Results

When choosing between single- and two-stage revision for hip prosthetic joint infection, surgeons considered multiple factors, including the patient context (age, ability to cope, carer responsibilities); patient preferences; primary prosthesis fixation; patient physiology (bone integrity and tissue damage, comorbidities, frailty); surgeon's knowledge, training and peer influence; local infrastructure (availability of microbiology, resources, costs); the infecting organism (clinicians' ability to identify, sensitivity to antibiotics); and duration of infection (acute or chronic). With evidence accruing on similar outcomes between surgical techniques, and observations of colleagues' successful use of single-stage revision, surgeons questioned whether or not revision in two stages remained the best treatment for hip prosthetic joint infection, and some were increasingly willing to consider more revisions in a single stage. Some surgeons managed uncertainty about the choice of surgical technique by using a CUMARS. Although single-stage revision was considered to be, potentially, the best strategy to treat hip prosthetic joint infection, surgeons thought that a change in practice was not yet justified. To inform any change in practice, surgeons noted the need for evidence from randomised trials. If there was no clear best strategy based on patient factors, their own knowledge and expertise, the available infrastructure and the infecting organism, then surgeons believed that the patients they treated would be eligible for randomisation.

Conclusions

With growing evidence of the success of treatment of hip prosthetic joint infection in a single stage, the willingness of some surgeons to change practice has increased over time. By using a CUMARS, surgeons were able to manage uncertainty about the choice between single- and two-stage revision. To guide treatment, surgeons identified the need for high-quality evidence to support their choice of revision strategy. Surgeons believed that a RCT comparing single- and two-stage revision for hip prosthetic joint infection is needed. While recognising that patient, infection, surgeon and infrastructure factors may indicate the need for a particular strategy, surgeons considered that randomisation would be feasible and acceptable.

Impact of cases of prosthetic knee infection on surgeons' personal and professional well-being

Here we present an overview of our published article.[61]

Aims

Although prosthetic joint infection has been described as 'an orthopaedic surgeon's worst nightmare',[62] relatively little is known about how prosthetic joint infection affects surgeons professionally and personally. We explored the impact of cases of knee prosthetic joint infection on surgeons' personal and professional well-being. The identification and acknowledgement of the emotional impact of prosthetic joint infection may help in developing support strategies and maintaining surgeons' well-being,[63] and a deeper understanding of the personal and professional impact of adverse events is needed.[64]

Methods

We conducted qualitative telephone interviews with consultant orthopaedic surgeons who treated patients for prosthetic knee infection in one of six high-volume NHS orthopaedic departments. The interviews were audio-recorded, transcribed, anonymised and imported into the qualitative data management software NVivo 10 for thematic analysis.[59]

Results

We interviewed 11 surgeons who had a mean of 9.5 years' experience as an orthopaedic consultant (range 1 month to 20 years). Surgeons perceived that being required to treat knee prosthetic joint infection was inevitable at some time in their career and this was a major concern, irrespective of their years of experience.

In our analyses we identified three themes that characterised the views and experiences of surgeons treating knee prosthetic joint infection: at some point, infection is inevitable but surgeons still feel accountable; the profound emotional impact; and supporting each other.

Participating surgeons described dealing with a diagnosis of prosthetic joint infection as 'devastating', 'soul-destroying' and 'deeply unpleasant'. Although they expected a diagnosis of prosthetic joint infection at some point in their career, its occurrence still made them question their practice, despite taking 'every measure', and left them feeling that they had let the patient down. Surgeons felt that empathy and honesty were important to patients who had received a diagnosis of prosthetic joint infection. They described how they needed to reflect carefully, questioning their practice, performance and surgical processes. To ensure that they maintained their confidence, surgeons felt that it was important to continue to perform surgery even after one of their patients had been diagnosed with prosthetic joint infection. Surgeons described their feelings of responsibility for patients' well-being and how they were motivated by the potential for relieving a patient's pain and improving quality of life, but that prosthetic joint infection could have serious consequences for a patient's quality of life. When prosthetic joint infection does occur, surgeons highlighted the importance of acknowledging the

diagnosis and being honest with patients. Our findings suggest that, in some departments, decisions about treatment may be made by surgeons individually and not always discussed with colleagues. Although the participants in the study felt supported by colleagues, one suggested that the occurrence of prosthetic joint infection could potentially be 'isolating' for a surgeon where such support did not exist.

Conclusion

Prosthetic joint infection has a considerable emotional impact on surgeons, who report a sense of devastation and personal ownership, particularly as they are largely unable to control its occurrence. Surgeons stressed the importance of a supportive multidisciplinary team in the management of prosthetic joint infection.

Risk factors for prosthetic hip or knee infection

Here we present an overview of five of our published articles.[50,51,65–67]

Background

The risk of developing prosthetic joint infection may be influenced by patient characteristics, the surgical intervention and postoperative care.

Aims

We aimed to identify risk factors for prosthetic joint infection after hip or knee replacement in new systematic reviews of published research and joint registry analyses.

Methods

Systematic reviews

Systematic reviews were registered prospectively with PROSPERO (CRD42015023485, CRD42018106503 and CRD42018114592) and conducted in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses)[68] and MOOSE (Meta-analysis Of Observational Studies in Epidemiology)[69] guidelines. We searched MEDLINE, EMBASE, Cochrane Library and reference lists, with no language restrictions (see *Appendices 3–5*).

In risk factor reviews, eligible studies included those with the following:

- patients with hip or knee replacement
- people with a potential risk factor
- comparator – non-exposed people
- outcome – prosthetic joint infection with ≥ 1 year of follow-up
- study – longitudinal study design.

In reviews of implant fixation, randomised trials with the following criteria were also included:

- patients with hip or knee replacement
- intervention – fixation
- control – alternative fixation
- outcome – prosthetic joint infection with ≥ 1 year of follow-up
- study – randomised design.

Searches were carried out on 1 September 2016 (general risk factors), 24 April 2019 (hip implant fixation) and 1 November 2018 (knee implant fixation).

In systematic reviews of fixation, we also included RCTs. Two investigators extracted study information and assessed quality using the Newcastle–Ottawa Scale,[70] with studies scoring ≥ 5 considered good quality. For RCTs, we used the Cochrane tool.[71] Study-specific relative risks (RRs) with 95% CIs were meta-analysed using random-effects models and grouped by study-level characteristics.

National Joint Registry analyses

We investigated the associations between potential risk factors and risk of revision for prosthetic joint infection after total hip and knee replacements recorded in the NJR. Primary procedures were performed between 2003 and 2013, with procedures subsequently revised for prosthetic joint infection up to 2014. Hospital activity and mortality were obtained through linkage with HES, the Patient Episode Database for Wales and the Office for National Statistics (ONS). Comorbidities were derived from the Charlson Comorbidity Index, as recorded in HES, using ICD-10 (*International Statistical Classification of Diseases and Related Health Problems*, Tenth Revision) codes.[50,51]

We investigated associations using Poisson multilevel models.[72] Regressions were adjusted for age, sex, ASA grade and body mass index (BMI). We reinvestigated associations in postoperative time periods using piecewise exponential multilevel models with period-specific effects.[73,74]

Results: systematic reviews

General risk factors

Searches identified 66 observational studies, including 512,508 participants with, predominantly, hip and knee replacement. The mean follow-up was 3.7 years (range 1–17 years). The risk of prosthetic joint infection was greater in men than in women (RR 1.36, 95% CI 1.18 to 1.57) and in smokers than in non-smokers (RR 1.83, 95% CI 1.24 to 2.70) (*Figure 4*). There were no associations between age or alcohol intake and the risk of prosthetic joint infection. One study reported a lower risk of prosthetic joint infection in patients living in rural locations than in those living in non-rural locations. The results of meta-analyses were consistent in higher-quality studies.

For BMI, there were consistent positive associations for comparisons with cut-off points of $\geq 30\,kg/m^2$ (*Figure 5*). Comparing BMI of $\geq 40\,kg/m^2$ with $< 40\,kg/m^2$, the pooled RR was 3.68 (95% CI 2.25 to 6.01). In one study, people with BMI $< 18.5\,kg/m^2$ had a greater risk of prosthetic joint infection than those with BMI of $18.5–30.0\,kg/m^2$.

Medical and surgical risk factors for prosthetic joint infection were diabetes, rheumatoid arthritis, depression, history of steroid administration and previous joint surgery. There was no evidence of important associations with osteoarthritis, osteonecrosis, post-traumatic arthritis, cardiovascular disease, hypertension, cancer, high-risk dental procedures or intra-articular steroid injections.

Hip implant fixation

Searches identified four RCTs (945 hip replacements) and 11 observational cohorts (2,260,428 hip replacements).

All RCTs were rated as being at a low risk of bias for random sequence generation and incomplete outcome data but at an unclear risk of bias in ≥ 1 other area. There were no clear differences in the risk of prosthetic joint infection when cemented fixations were compared with uncemented or reverse hybrid fixations (*Figure 6*). In one RCT,[75] the risk of prosthetic joint infection was lower in patients receiving implant fixation with antibiotic-loaded cement than in those receiving it with plain cement.

In a pooled analysis of observational studies, any fixation with cement was associated with an increased risk of prosthetic joint infection compared with uncemented fixation. In studies with higher quality scores, the difference favouring uncemented over cemented fixation was consistent (RR 1.09, 95% CI 1.03 to 1.16).

Compared with antibiotic-loaded cemented fixations, plain cemented fixations were associated with an increased risk of prosthetic joint infection (RR 1.52, 95% CI 1.36 to 1.70).

Comparisons	Number of studies	Number of participants	Number of cases		RR (95% CI)
Males vs. females	28	349,950	5377		1.36 (1.18 to 1.57)
Smokers vs. non-smokers	8	20,689	385		1.83 (1.24 to 2.70)
Per 1-year increase in age	8	171,254	1469		0.99 (0.98 to 1.00)
High alcohol intake vs. no high alcohol intake	2	41,043	1395		2.84 (0.81 to 10.02)
Age ≥ 65 years vs. < 65 years	1	3672	47		0.99 (0.55 to 1.77)
Rural vs. non-rural location	1	71,793	637		0.77 (0.61 to 0.97)

RR (95% CI)

0.5 0.75 1   2.5   5 7.5   15

FIGURE 4 Sociodemographic characteristics and risk of prosthetic joint infection.

BMI comparisons (kg/m²)	Number of studies	Number of participants	Number of cases		RR (95% CI)
≥ 40 vs. < 40	5	24,134	187		3.68 (2.25 to 6.01)
≥ 35 vs. < 35	2	56,803	492		1.53 (1.22 to 1.92)
≥ 30 vs. < 30	20	92,240	2311		1.60 (1.29 to 1.99)
≥ 25 vs. < 25	4	18,492	274		1.02 (0.68 to 1.52)
Per unit increase	2	1335	80		1.09 (0.92 to 1.29)

```
        0.5  0.75  1  1.5   2.5    5   7.5
                    RR (95% CI)
```
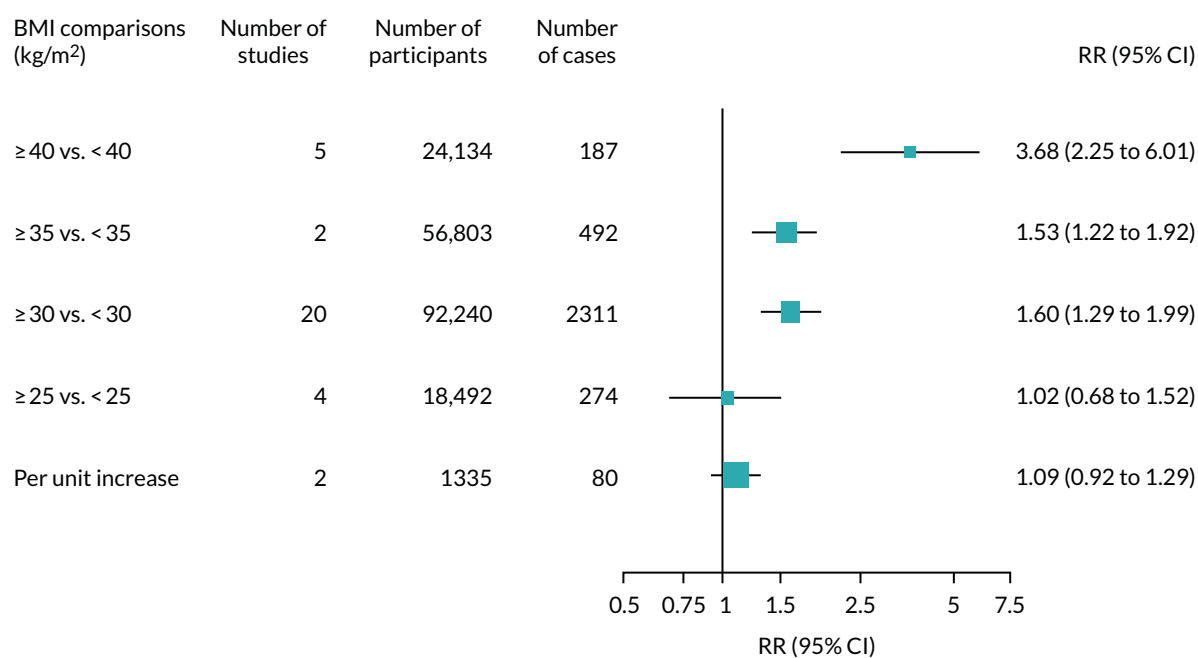
FIGURE 5 Body mass index and risk of prosthetic joint infection.

Knee implant fixation

Searches identified eight RCTs (4029 knee replacements) and 24 observational studies (1,161,292 knee replacements).

Randomised controlled trials were rated as being at low risk of bias for incomplete outcome data and selective reporting. Four were rated as being at an unclear risk of bias for allocation concealment. There was no difference in the risk of prosthetic joint infection when uncemented fixation was compared with cemented or hybrid fixation and when hybrid fixation was compared with cemented fixation (*Figure 7*). In one trial[76] that randomised 2948 patients, there was no difference in the risk of prosthetic joint infection when antibiotic-loaded cemented fixation was compared with plain cemented fixation.

In a pooled analysis of observational studies, uncemented fixation was associated with a decreased overall risk of prosthetic joint infection compared with cemented fixation (RR 0.76, 95% CI 0.64 to 0.89). The results of meta-analyses were consistent in higher-quality studies. There was no difference in overall risk of prosthetic joint infection for antibiotic-loaded cemented fixation compared with plain cement.

Results: National Joint Registry analyses

Risk factors for revision of hip replacement for prosthetic joint infection

Of 623,253 primary hip replacements carried out between 2003 and 2013 and with ≥ 1 year of follow-up [median 4.6 years, interquartile range (IQR) 2.6–7.0 years], 2705 were revised for prosthetic joint infection. The incidence rate ratios for revision are summarised by patient, surgical and health system characteristics in *Appendices 6–8*.

Patient characteristics

People aged ≥ 80 years were at lower risk of revision for hip prosthetic joint infection than people aged < 60 years (RR 0.66, 95% CI 0.56 to 0.76) (*Figure 8*). Men were at higher risk of revision of hip prosthetic joint infection than women (RR 1.68, 95% CI 1.56 to 1.81). The numbers of revisions in ethnic minority groups were small, and we were unable to investigate ethnicity as a possible risk factor. People with a BMI of ≥ 30 kg/m² had a higher risk of revision for hip prosthetic joint infection

Fixation comparison	Number of studies	Number of patients/hips	Number of prosthetic joint infections		RR (95% CI)
Observational cohort studies					
All cemented vs. uncemented	10	1,308,868	7281		1.10 (1.04 to 1.17)
Plain cemented vs. uncemented	3	527,702	3164		1.50 (1.27 to 1.77)
Antibiotic-loaded cemented vs. uncemented	3	568,771	3526		1.07 (0.97 to 1.18)
Plain cemented vs. antibiotic-loaded cemented	3	687,220	3524		1.52 (1.36 to 1.70)
Hybrid vs. uncemented	6	779,526	4318		1.49 (1.36 to 1.64)
Hybrid vs. all cemented	2	36,626	403		1.10 (0.81 to 1.49)
Reverse hybrid vs. uncemented	2	349,231	1005		1.49 (1.14 to 1.95)
Reverse hybrid vs. all cemented	1	496,567	2309		1.18 (1.04 to 1.34)
RCTs					
All cemented vs. uncemented	2	400	4		5.04 (0.59 to 42.75)
Plain cemented vs. antibiotic-loaded cemented	1	476	15		5.56 (1.55 to 19.91)
Reverse hybrid vs. all cemented	1	69	1		3.09 (0.13 to 73.33)

RR (95% CI)

FIGURE 6 Fixation types and risk of hip prosthetic joint infection in observational studies and RCTs.

Fixation comparison	Number of studies	Number of patients/hips	Number of prosthetic joint infections		RR (95% CI)
Observational cohort studies					
Uncemented vs. cemented	8	892,094	4118		0.76 (0.64 to 0.89)
Uncemented vs. hybrid	2	4291	4		1.08 (0.16 to 7.51)
Hybrid vs. cemented	6	109,055	892		0.98 (0.80 to 1.21)
Antibiotic-loaded cement vs. plain cement	12	200,442	1039		0.95 (0.69 to 1.31)
RCTs					
Uncemented vs. cemented	3	609	13		0.81 (0.28 to 2.36)
Uncemented vs. hybrid	3	342	9		0.90 (0.26 to 3.11)
Hybrid vs. cemented	1	130	1		3.00 (0.12 to 72.32)
Antibiotic-loaded cement vs. plain cement	1	2948	85		1.22 (0.80 to 1.86)

0.1 0.25 0.75 1   2.5 5   15 25 50 75

RR (95% CI)

FIGURE 7 Fixation types and risk of knee prosthetic joint infection in observational studies and RCTs.
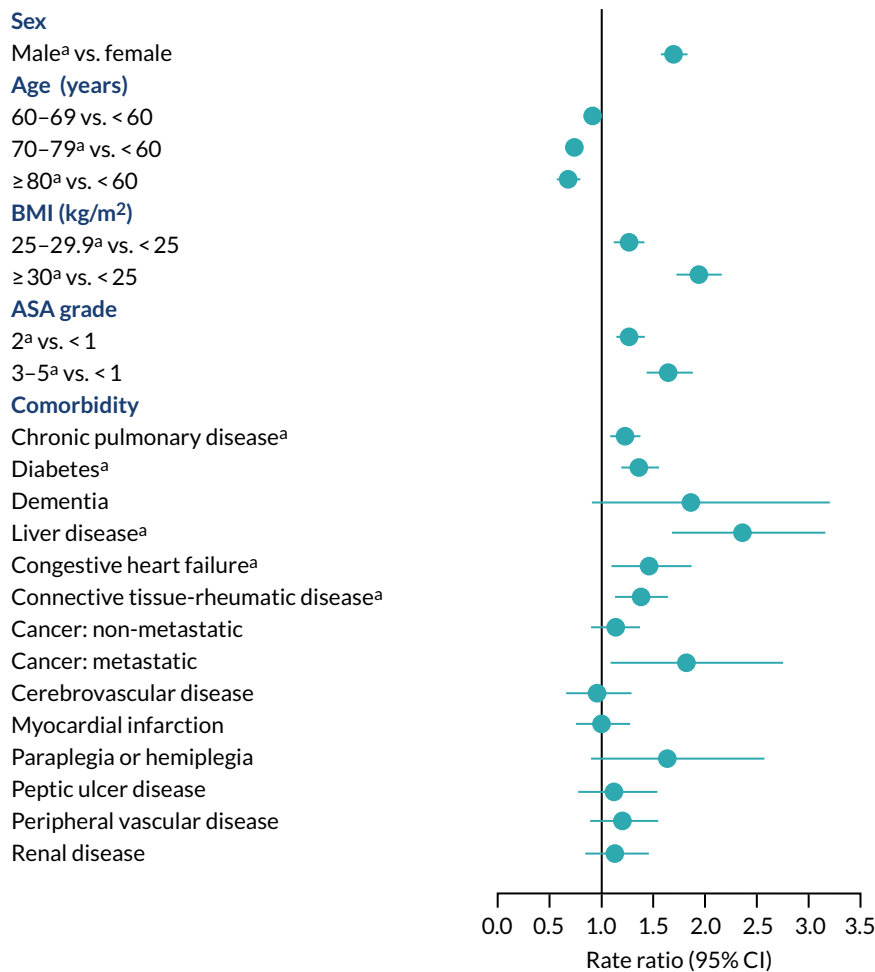
FIGURE 8 Patient characteristics and risk of revision for hip prosthetic joint infection during the whole postoperative period: NJR analysis. Reference category in parentheses. a, Adjusted p-value < 0.05.

than those with a BMI of < 25 kg/m² (RR 1.92, 95% CI 1.72 to 2.15). People with diabetes, chronic pulmonary disease, congestive heart failure, connective tissue-rheumatic disease, previous septic arthritis or fractured neck of femur had a higher risk of revision for hip prosthetic joint infection. More generally, people with greater medical comorbidity had a higher risk of revision for hip prosthetic joint infection (ASA grades 3–5 vs. ASA grade 1: RR 1.63, 95% CI 1.42 to 1.87). In the first 3 months after primary hip replacement, the risk of revision for hip prosthetic joint infection was higher for people with dementia than for those without (RR 3.78, 95% CI 1.21 to 7.81). People with liver disease had an increased risk of revision for hip prosthetic joint infection but only at ≥ 2 years after primary hip replacement (RR 2.43, 95% CI 1.35 to 3.82). There were no clear associations between cardiovascular disease, cerebrovascular disease, myocardial infarction, peripheral vascular disease, cancer (except metastatic disease) and paraplegia or hemiplegia and the risk of revision for hip prosthetic joint infection.

Surgical factors

Compared with unaffected people, those with osteoarthritis or congenital hip dysplasia were at lower risk, while people treated for fractured neck of femur or osteonecrosis were at higher risk of revision for hip prosthetic joint infection (*Figure 9*). There was a particularly high risk of further infection in those who had experienced a previous hip infection (RR 6.69, 95% CI 4.18 to 9.80). The use of the lateral surgical approach was associated with an increased risk of revision for hip prosthetic joint infection compared with the posterior approach (RR 1.32, 95% CI 1.21 to 1.43). Up until 2 years after hip replacement, the risk with metal-on-metal bearing combinations was lower than or similar to
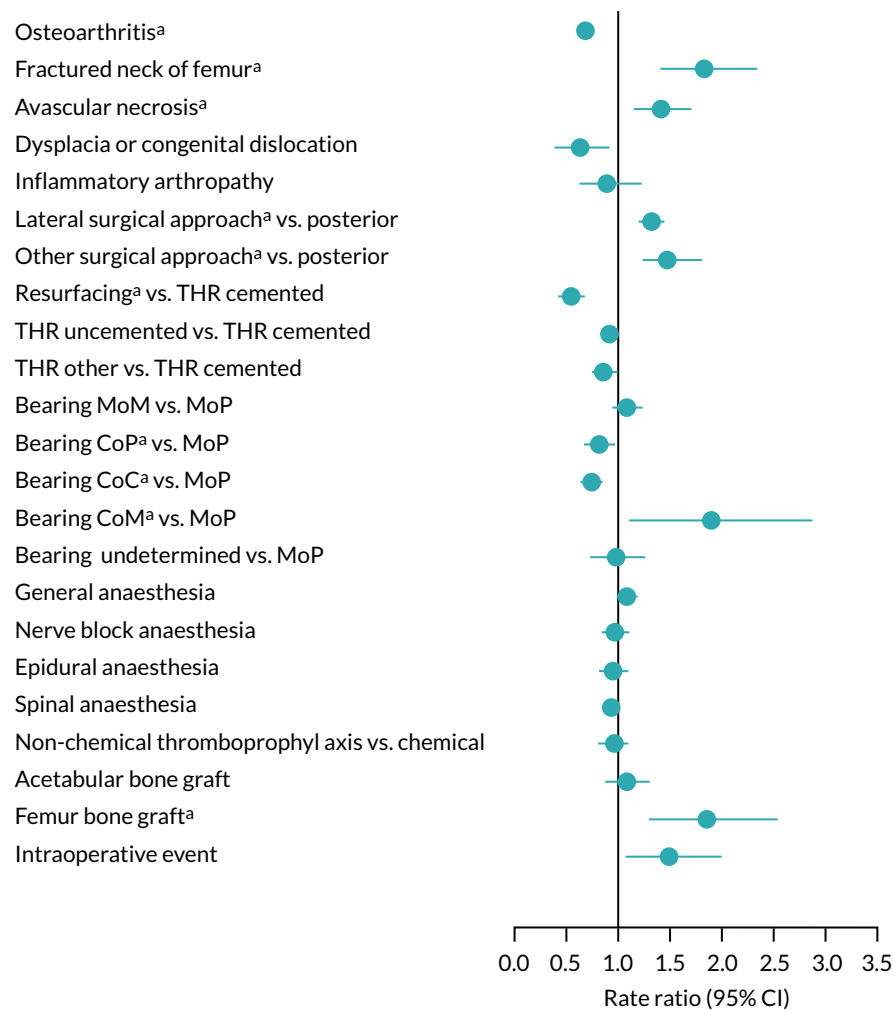
FIGURE 9 Surgical factors and risk of revision for hip prosthetic joint infection during the whole postoperative period: NJR analysis. Reference category in parentheses. a, Adjusted *p*-value < 0.05. CoC, ceramic-on-ceramic; CoM, ceramic-on-metal; CoP, ceramic-on-polyethylene; MoM, metal-on-metal; MoP, metal-on-polyethylene; THR, total hip replacement.

that with metal-on-polyethylene, but at longer follow-up the risk was higher with metal-on-metal. Ceramic-on-ceramic and ceramic-on-polyethylene bearing combinations were associated with a lower risk of revision after 24 months than metal-on-polyethylene bearings. Little or no difference in the risk of revision for hip prosthetic joint infection was found for anaesthetic technique, thromboprophylaxis regime, the use of acetabular bone graft or intraoperative complication. Patients with a femoral bone graft during primary hip replacement were at higher risk of revision for hip prosthetic joint infection.

Health system factors

The risk of revision for hip prosthetic joint infection was similar in Wales and England and did not differ according to funding source, operating surgeon grade or consultant surgeon presence during surgery (*Figure 10*). Operating surgeons who performed more hip replacements annually had a lower risk of revision for hip prosthetic joint infection than surgeons with a lower volume. The volume of all hip procedures carried out by the surgeon in charge of the surgery did not affect the risk of revision. The risk of revision for hip prosthetic joint infection was higher in the first 3 months after primary surgery in hospitals that had performed over 255 hip procedures in the year before primary surgery than in hospitals with a small volume of activity. No specific difference in the rate ratios were found beyond this period or for units with lower volumes of hip procedures.
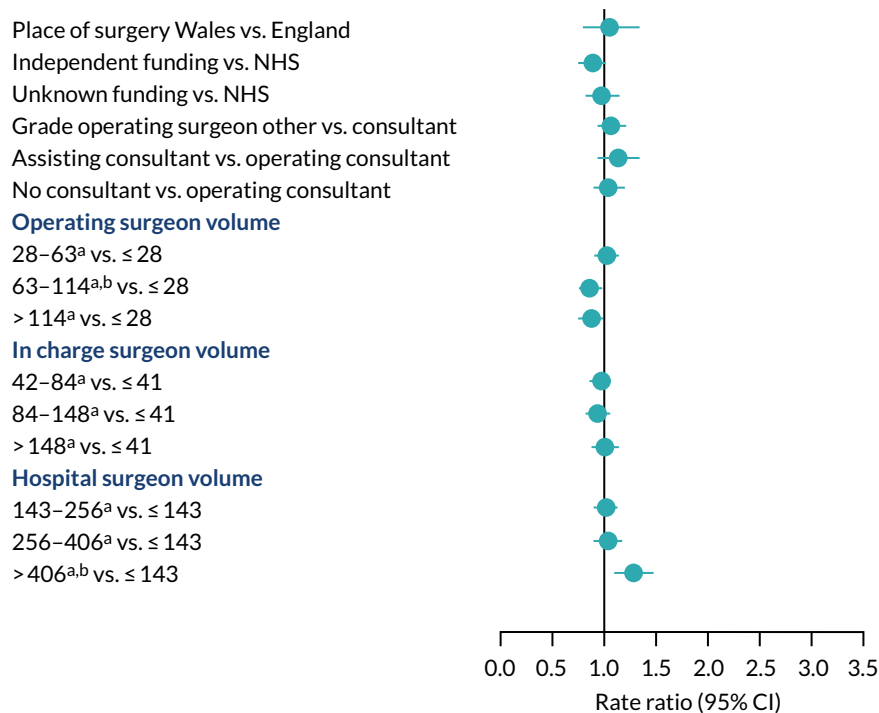
FIGURE 10 Health system factors and risk of revision for hip prosthetic joint infection during the whole postoperative period: NJR analysis. Reference category in parentheses. a, Volume is the total number of hip replacements performed in the previous 12 months; b, adjusted *p*-value < 0.05.

Risk factors for revision of knee replacement for prosthetic joint infection

Between 2003 and 2015, 679,010 primary knee replacements were recorded in the NJR, of which 3659 were revised for prosthetic joint infection at ≥ 1 year follow-up (median 4.6 years, IQR 2.6–6.9 years). After primary knee replacement, incidence rate ratios of revision for prosthetic joint infection are summarised for different patient, surgical and health system characteristics in *Appendices 9–11*.

Patient characteristics

People aged ≥ 80 years were less likely to have a revision for knee prosthetic joint infection than those aged < 60 years (RR 0.50, 95% CI 0.43 to 0.57) (*Figure 11*). Men were more likely than women to have a revision for knee prosthetic joint infection (RR 1.83, 95% CI 1.71 to 1.96). There were too few revisions for knee prosthetic joint infection in ethnic minority groups to investigate ethnicity as a possible risk factor. The likelihood of revision for knee prosthetic joint infection was higher in people with a BMI of ≥ 30 kg/m^2 than in those with a BMI of < 25 kg/m^2 (RR 1.46, 95% CI 1.29 to 1.63). The risk of revision for knee prosthetic joint infection was higher in people with more medical comorbidities, and specifically in people with diabetes, chronic pulmonary disease, connective tissue and rheumatic diseases and peripheral vascular disease. An elevated risk in people with liver disease was specific to the period after 2 years.

Surgical factors

Aspects of surgery associated with an increased risk of revision for prosthetic joint infection after knee replacement were surgery for trauma, previous knee infection, inflammatory arthropathy, operation under general anaesthesia, requirement for tibial bone graft and use of posterior stabilised fixed-bearing prostheses compared with unconstrained fixed-bearing prostheses and constrained condylar prostheses (*Figure 12*). Compared with cemented total knee replacement, lower rates of prosthetic joint infection were seen in people who received uncemented, unicondylar or patellofemoral knee replacement.
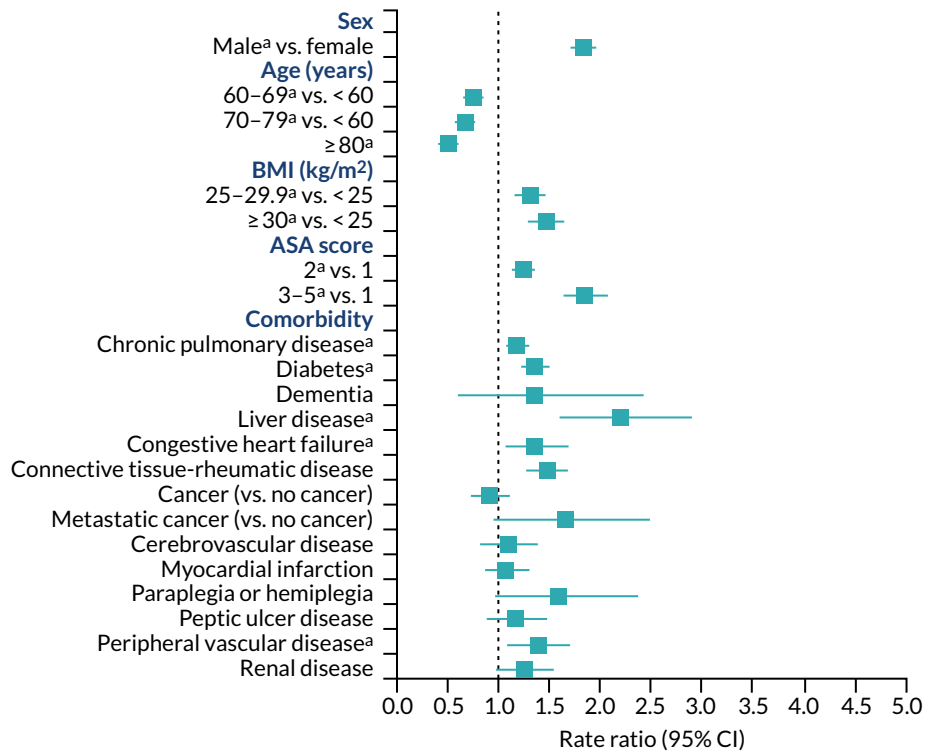
FIGURE 11 Patient characteristics and risk of revision for knee prosthetic joint infection during the whole postoperative period: NJR analysis. a, Adjusted *p*-value < 0.05.
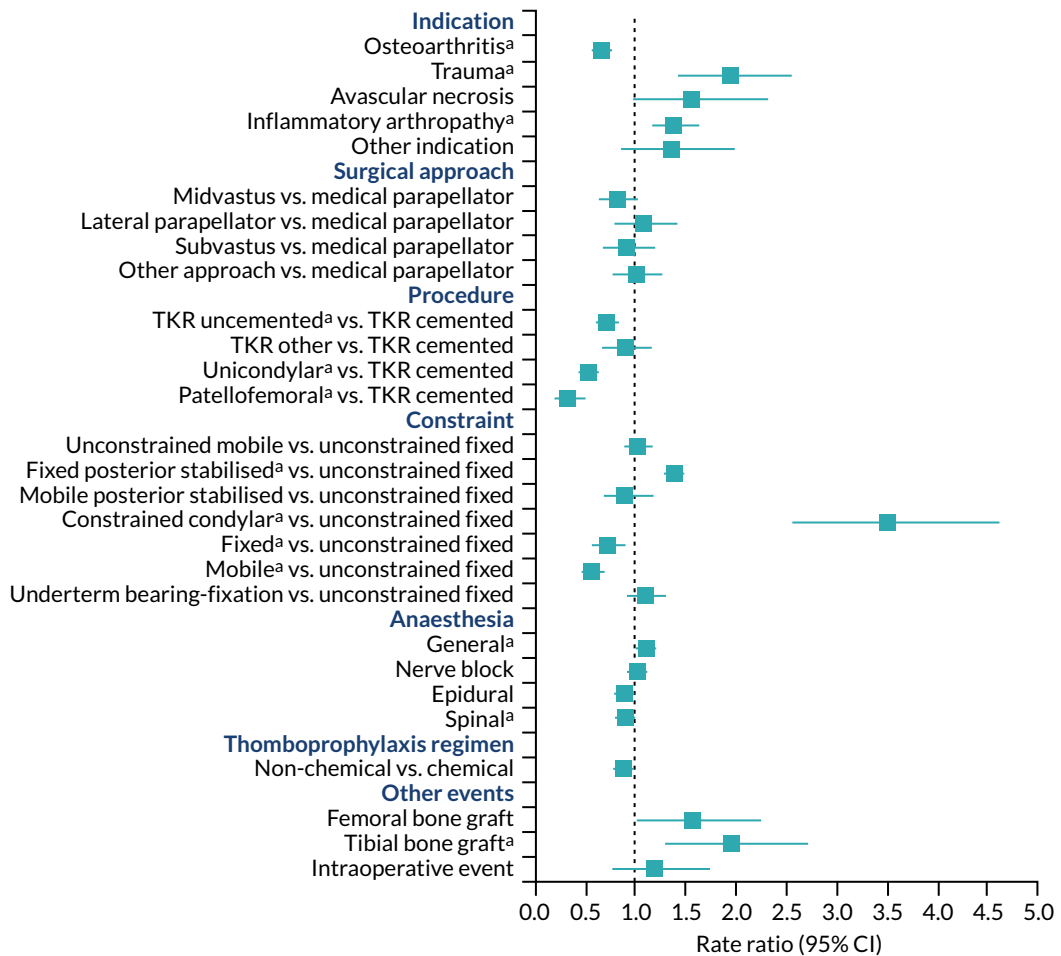
FIGURE 12 Surgical factors and risk of revision for knee prosthetic joint infection during the whole postoperative period: NJR analysis. a, Adjusted *p*-value < 0.05.

Health system factors

The risk of revision for prosthetic joint infection after knee replacement was similar in Wales and England (*Figure 13*). Privately funded procedures had a lower risk of revision than procedures funded by the NHS. Revision for knee prosthetic joint infection was not affected by the operating surgeon's grade, the presence of a consultant surgeon during surgery, or the volume of knee procedures carried out by the operating surgeon or the surgeon in charge. The risk of revision for knee prosthetic joint infection was higher in high-volume hospitals than in low-volume hospitals. In hospitals that had carried out more than 440 knee procedures in the year preceding the index surgery, the risk of revision for prosthetic joint infection was higher in the first 3 months after surgery than in hospitals with a small volume of activity.

Discussion

The two research approaches complemented each other as cohort studies included in systematic reviews and the NJR reported associations between a diverse range of potential risk factors and risk of prosthetic joint infection and need for revision.

Risk of hip and knee prosthetic joint infection and need for revision is higher in men, people with a high BMI, people with diabetes and those receiving implants with cemented fixation. In the NJR an association was noted between dementia and increased early risk of revision for hip prosthetic joint infection.

Meta-analysis of cohort studies showed no association with age, but in the NJR, younger patients were at higher risk of revision for hip or knee prosthetic joint infection. This may be because the NJR had a longer follow-up with more time for joint infections to occur in younger patients. Older people at high risk of adverse outcomes and death from surgery may have received non-operative management. NJR data show not the risk of infection, but the risk of revision for infection. It may be that clinicians are more likely to treat older patients with suppressive antibiotics than with surgery. In NJR analyses, people with more medical comorbidities had an increased risk of revision for hip and knee prosthetic joint infection, and this was noted for specific conditions in meta-analyses and NJR analysis.
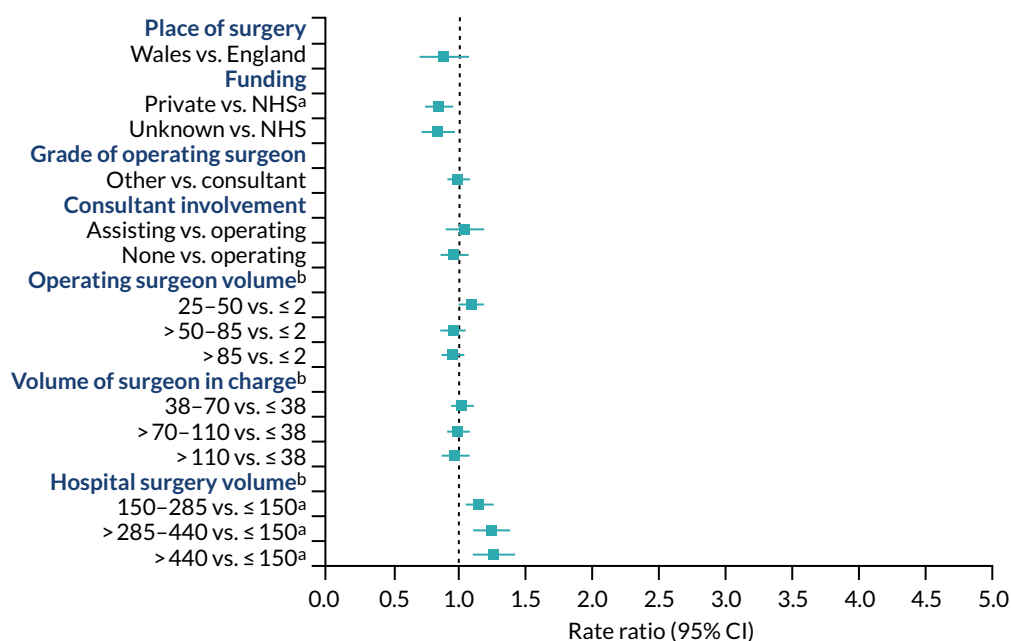
FIGURE 13 Health service factors and risk of revision for knee prosthetic joint infection during the whole postoperative period: NJR analysis. a, Adjusted *p*-value < 0.05; b, volume is the total number of knee replacements performed in the previous 12 months.

Analyses provide reassurance that many surgical and health system factors do not increase the risk of prosthetic joint infection. There was a suggestion that the posterior approach and use of ceramic-on-ceramic and ceramic-on-plastic bearings had a lower risk of infection after hip replacement.

Limitations

In meta-analyses, definitions of prosthetic joint infection and the adjustment for confounding factors differed between studies. The results of meta-analyses were consistent in higher-quality studies and we noted no differences in studies reporting univariable or multivariable analyses.

The NJR analyses relied on subjective diagnosis of prosthetic joint infection by individual surgeons. As with our meta-analyses, there may have been residual confounding factors and associations may vary with different causative pathogens. For example, older people may be at higher risk of infection with organisms that are difficult to treat.[77]

With observational data such as those collected in the NJR and cohort studies included in our systematic reviews, we cannot establish for certain whether or not the relationships between risk factors and revision for prosthetic joint infection are causal.

Diagnosis of prosthetic joint infection: assessment of new methods

Here we present an overview of our published article.[78]

Aims

We aimed to assess the diagnostic accuracy of promising synovial biomarkers for prosthetic joint infection: the alpha-defensin immunoassay and leucocyte esterase colorimetric strip test.

Methods

The systematic review was registered with PROSPERO (CRD42015023704) and conducted in accordance with PRISMA and diagnostic test accuracy guidelines.[68,79] We searched MEDLINE and EMBASE on Ovid from inception until 30 May 2015 (see *Appendix 12*).

Inclusion criteria were:

- people with hip or knee replacement suspected of having a prosthetic joint infection but with true diagnostic uncertainty
- measurements of synovial fluid alpha-defensin or leucocyte esterase
- prosthetic joint infection according to Musculoskeletal Infection Society (MSIS) diagnostic criteria or confirmation during subsequent surgery
- reports of diagnostic test accuracy.

Screening and data extraction were performed independently by two reviewers. Extracted data related to patient characteristics, hip or knee joint, diagnostic test, test cut-off points, reference standards and results (sensitivity, specificity and likelihood ratios). Sensitivity and specificity values from each evaluation were pooled using a bivariate meta-analysis framework.[80] A quality assessment of each study was performed using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool.[81]

Results

We included 11 eligible studies. The mean QUADAS-2 score was 13 out of 14 (range 11–14), suggesting that the studies were of good quality. The pooled diagnostic sensitivity and specificity of synovial fluid alpha-defensin (six studies) for prosthetic joint infection were 1.00 (95% CI 0.82 to 1.00) and 0.96 (95% CI 0.89 to 0.99), respectively. The area under the curve (AUC) was 0.99 (95% CI 0.98 to 1.00).

The pooled diagnostic sensitivity and specificity of leucocyte esterase (five studies) for prosthetic joint infection were 0.81 (95% CI 0.49 to 0.95) and 0.97 (95% CI 0.82 to 0.99), respectively. The AUC was 0.97 (95% CI 0.95 to 0.98).

There was substantial heterogeneity among studies for both diagnostic tests. No studies reported cost-effectiveness.

Discussion

Synovial fluid alpha-defensin and leucocyte esterase showed high diagnostic accuracy for prosthetic joint infection. Alpha-defensin was extremely sensitive and specific in the identification of prosthetic joint infection. Leucocyte esterase was slightly less sensitive but was extremely specific in the identification of prosthetic joint infection.

A systematic review published in 2019 considered a broad range potential serum, synovial and tissue diagnostic tests for prosthetic joint infection.[82] Of 83 tests identified, 17 had enough data from studies to allow meta-analysis. The authors reached similar conclusions to ours in identifying synovial fluid alpha-defensin and leucocyte esterase as the best-performing diagnostic tests for prosthetic joint infection.

Cost implications of the tests vary considerably. In a UK report, the lateral flow tests for alpha-defensin cost £300 each when purchased in a pack of five.[83] The laboratory-based immunoassay costed within a suite of tests was £450. This compares with a cost of £0.11 for a leucocyte esterase test.[78]

Since the publication of our study, the MSIS criteria have reported a new definition of prosthetic joint infection citing our systematic review (*Figure 14*).[84] These include a definition that a hip or knee is infected if synovial leucocyte esterase is elevated and alpha-defensin is positive.

Limitations

Our study was limited by the small number of studies in the systematic review. Thus, we were not able to assess publication bias, and four out of six studies of alpha-defensin were conducted by a research group who held patents relating to the test.

Major criteria (at least one of the following)	Decision
Two positive cultures of the same organism	Infected
Sinus tract with evidence of communication to the joint or visualisation of the prosthesis	

		Minor criteria	Score	Decision
Preoperative diagnosis	Serum	Elevated CRP or D-dimer	2	≥ 6 infected
		Elevated ESR	1	
	Synovial	Elevated synovial WBC count or LE	3	2–5 possibly infected[a]
		Positive alpha-defensin	3	
		Elevated synovial PMN (%)	2	0–1 not infected
		Elevated synovial CRP	1	

	Inconclusive pre-operative score or dry tap[a]	Score	Decision
Intraoperative diagnosis	Preoperative score	–	≥ 6 infected
	Positive histology	3	4–5 inconclusive[b]
	Positive purulence	3	
	Single positive culture	2	≤ 3 not infected

FIGURE 14 The 2018 MSIS criteria for prosthetic joint infection. a, For patients with inconclusive minor criteria, operative criteria can also be used to fulfill definition for PJI; b, consider further molecular diagnostics such as next-generation sequencing. Note: proceed with caution in adverse local tissue reaction, crystal deposition disease and slow-growing organisms. CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; LE, leukocyte esterase; PMN, polymorphonuclear; WBC, white blood cell. Reprinted from *The Journal of Arthroplasty*, Vol. 33, Parvizi J, Tan TL, Goswami K, Higuera C, Della Valle C, Chen AF, Shohat N. The 2018 definition of periprosthetic hip and knee infection: an evidence-based and validated criteria. pp. 1309–14. Copyright 2018, with permission from Elsevier.

Surgical treatment of prosthetic joint infection: evidence from cohort studies

Here we summarise three of our systematic reviews,[85–87] our IPD meta-analysis[88] and our NJR analyses (see *Appendix 13*).

Aims

In systematic reviews and meta-analyses, we aimed to compare reinfection rates after single- and two-stage treatments of hip and knee prosthetic joint infection. In an IPD meta-analysis we aimed to compare reinfection outcomes after single- and two-stage treatment of hip prosthetic joint infection. In a meta-analysis we aimed to assess the risk of reinfection after treatment of prosthetic joint infection with DAIR.

Analyses of linked NJR/ONS data aimed to compare rates of reinfection and mortality for people with prosthetic joint infection treated with single- or two-stage revision.

Methods: systematic reviews

The systematic reviews were registered prospectively with PROSPERO (CRD42017057513, CRD42015016559 and CRD42015017327) and conducted according to PRISMA[68] and MOOSE[69] guidelines. We searched MEDLINE and EMBASE on Ovid and Web of Science from inception (see *Appendices 14–16*), and reference lists.

Eligible studies included:

- unselected patients with hip or knee prosthetic joint infection
- treatment with DAIR, or single- or two-stage revision
- reinfection or new infection outcome within 2 years of single- or two-stage revision, or any time after DAIR
- longitudinal design.

We excluded studies that reported case series of selected patients, for example those with a specific infection; studies with fewer than 10 patients; and, for studies of single- and two-stage revision, follow-up of < 2 years.

Searches were carried out on 1 May 2017 (DAIR), 1 March 2015 (hip single- or two-stage revision) and 1 August 2015 (knee single- or two-stage revision).

Methodological quality was assessed using MINORS (methodological index for non-randomized studies).[89] The rate of reinfection within 2 years was the primary outcome across studies. Pooled rates were calculated using the Freeman–Tukey variance-stabilising double arcsine transformation.[90] Publication bias was assessed using Egger's regression symmetry tests.[91]

Methods: individual patient data meta-analysis

The IPD meta-analysis protocol was registered on PROSPERO (CRD42015016664) and conducted as recommended by the Cochrane Collaboration,[92] the guidance of Riley *et al.*[93] and the PRISMA-IPD guidelines.[94] The study was limited to studies reporting outcomes after single- and two-stage revision

for hip prosthetic joint infection. Searches[86] were updated in August 2016. Authors of eligible studies and well-known investigators in the field were contacted, provided with the study protocol and invited to join the Global INFORM collaboration.[95] Collaborators were provided with standardised spreadsheets that were combined into a single database. Data in published articles were also included.

The risks of reinfection were compared using Cox proportional shared frailty models.[96] Hazard ratios (HRs) with 95% CIs were calculated, with progressive adjustment for age, sex, Charlson Comorbidity Index, previous hip surgery and type of infecting organism ('difficult to treat' vs. 'not difficult to treat').

Methods: National Joint Registry analysis

As described in *Appendix 13*, we analysed NJR data for England and Wales collected between 2003 and 2014 linked with ONS data. We included patients with a primary hip or knee replacement that had subsequently been revised for prosthetic joint infection with either a single- or a two-stage procedure. Reinfection and mortality outcomes were compared between treatment of hip and knee prosthetic joint infection using single- and two-stage revision strategies, and for mortality also with primary hip and knee replacements, and aseptic revisions. Analyses were adjusted for age, sex and ASA grade.

Results: systematic reviews

DAIR
We included 99 observational studies with data on 4897 prosthetic joint infections treated with DAIR. The infection control rate for DAIR ranged from 11.1% to 100%, with an overall pooled estimate of 61.4% (95% CI 57.3% to 65.4%). Infection control rates were poorer in patients aged < 70 years, in knee compared with hip prosthetic joint infection, in late chronic infections and in DAIR conducted before 2000.

Single-stage compared with two-stage revision for hip prosthetic joint infection
No randomised trials were identified. An assessment of reinfection outcomes was reported after single-stage revision in 38 studies ($n = 2536$ patients) and after two-stage revision in 60 studies ($n = 3288$ patients). MINORS methodological quality scores ranged from 9 to 16. The median age of participants was 63 years in single-stage studies and 60 years in two-stage studies.

The rate of reinfection was 8.2% (95% CI 6.0% to 10.8%) after single-stage revision and 7.9% (95% CI 6.2% to 9.7%) after two-stage revision. Reinfection rates remained generally similar when grouped by several study- and population-level characteristics.

Single-stage compared with two-stage revision for knee prosthetic joint infection
Searches identified no RCTs. Reinfection outcomes were reported after single-stage revision in 10 studies ($n = 423$ patients) and after two-stage revision in 108 studies ($n = 5129$ patients). MINORS methodological quality scores ranged from 9 to 15. The median age of participants was 71 years in single-stage studies and 67 years in two-stage studies.

In single-stage cohorts, the rate of reinfection was 7.6% (95% CI 3.4% to 13.1%), compared with 8.8% (95% CI 7.2% to 10.6%) in two-stage cohorts. Reinfection rates remained generally similar in several study-level and clinical characteristic subgroups. There was evidence of publication bias in two-stage studies.

Results: individual patient data meta-analysis

Eighty-five articles were identified reporting 98 cohorts of patients with hip prosthetic joint infection published up to August 2016. Contact with authors of studies led to the Global INFORM collaboration, comprising 15 cohorts ($n = 1383$ patients) with author-provided data. Data from a further 29 studies ($n = 473$ patients) were extracted from published articles.

After a median follow-up of 3.7 years, 222 reinfections were recorded. Reinfection rates per 1000 person-years of follow-up were 16.8 (95% CI 13.6 to 20.7) and 32.3 (95% CI 27.3 to 38.3) for single- and two-stage procedures, respectively. Among individuals with available data, the age-adjusted HR for reinfection comparing two- with single-stage revision was 1.69 (95% CI 0.58 to 4.98; $p = 0.338$). Progressive adjustment for sex, previous hip surgery and comorbidities did not change the outcome.

Results: National Joint Registry analysis

Hip prosthetic joint infection
Between 2003 and 2014, 535 patients with hip prosthetic joint infection received a single-stage revision and 1605 received a two-stage revision. More patients who received a single-stage revision had a re-revision for prosthetic joint infection in the first 2 years (HR 1.70, 95% CI 1.19 to 2.44; $p = 0.004$). This difference was limited to the first 3 months after surgery (HR 1.81, 95% CI 1.22 to 2.68; $p = 0.003$). For all-cause re-revision, the 2-year HR was 1.54 (95% CI 1.15 to 2.07; $p = 0.004$), which again was limited to the first 3 months after surgery.

Patients who received an initial single-stage revision had, on average, fewer revision operations than those who received a two-stage revision (1.3 vs. 2.2; $p < 0.0001$). Mortality rates were comparable between single- and two-stage procedures (29/10,000 person-years vs. 33/10,000 person-years), but these rates were higher than those observed after primary hip replacement or aseptic revision.

Knee prosthetic joint infection
Between 2003 and 2013, 489 patients with knee prosthetic joint infection received a single-stage revision and 2377 received a two-stage revision. The rates of revision for reinfection in the first 2 years were similar (HR 1.09, 95% CI 0.76 to 1.57; $p = 0.66$), and this was consistent at all follow-up time points. There was weak evidence of an increased risk of re-revision for any cause after single-stage revision (HR 1.32, 95% CI 0.97 to 1.81; $p = 0.08$), and this was limited to the first 3 months after revision for knee prosthetic joint infection (HR 1.51, 95% CI 0.95 to 2.41; $p = 0.08$).

Patients who received an initial single-stage revision had, on average, fewer revision procedures than those who received a two-stage revision (1.2 vs. 2.2; $p < 0.001$). Mortality was lower for single-stage revision between 6 and 18 months post operation (adjusted HR at 6 months 0.51, 95% CI 0.25 to 1.00; $p = 0.05$).

Conclusion

DAIR may be effective for > 60% of patients, particularly if it is performed early. An analysis of the NJR showed a higher risk of re-revision following single-stage revision for hip prosthetic joint infection than following two-stage revision, but this was limited to the 3 months after revision surgery. Patients who received a a single-stage revision had a smaller number of operations. When considered alongside the results of meta-analyses, the single-stage revision strategy for hip prosthetic joint infection is a reasonable option, with acceptable rates of infection control. Re-infection rates after single- and two-stage revision for knee prosthetic joint infection were similar, and patients who received single-stage revision underwent considerably fewer operations.

Limitations

An important limitation is that people may have been selected for a revision strategy depending on patient factors, including health status. An IPD meta-analysis was limited by a lack of available data for clinically relevant subgroups, including BMI and outcomes such as early or late infection. Our comparison of outcomes in cohorts of knee prosthetic joint infection was limited because few studies have reported outcomes after single-stage revision. Few studies collected patient-reported outcomes.

In the NJR studies there were small differences in patient characteristics between groups, which may indicate a degree of selection bias, and this may differ between the hip and knee cohorts. Furthermore, there is no linkage with microbiological data, and patients may have received a revision strategy based on the virulence of the infecting organism.

Surgical treatment of prosthetic joint infection: the INFORM randomised controlled trial

Here we summarise the INFORM randomised trial methods[97] and results (see *Appendix 17*).

Aims

Our aim was to determine whether or not there is a difference in patient-reported outcome 18 months after randomisation to single- or two-stage revision surgery for the treatment of hip prosthetic joint infection. Eighteen months was chosen because the median interval between the stages of a two-stage revision is about 105 days (IQR 70–173 days), and, therefore, most people receiving a two-stage surgery should have achieved maximum recovery. A longer follow-up may have limited recruitment and patient retention. Although the trial was not powered to compare rates of reinfection or occurrence of a new infection, adverse events were monitored.

Methods

INFORM was a multicentre, two-arm, parallel-group, participant and observer unblinded, randomised superiority trial (ISRCTN Registry number ISRCTN10956306). Full details are in the published protocol[97] and at https://doi.org/10.5523/bris.2323q1mtahy6y2dy5ua3opivqf. Patients deemed by their treating surgeons and multidisciplinary prosthetic joint infection teams to have infected hip replacements were randomised to either a single- or a two-stage revision.

Trial oversight
The protocol was approved by the UK National Research Ethics Committee South West and the University of Gothenburg review board. An independent steering committee and a data monitoring committee oversaw the study.

Sample size
The study sample size was based on our previous RCT of hip replacement.[98] To show a 10-point difference (equivalent to a standard deviation of 0.5) in total Western Ontario and McMasters Universities Osteoarthritis Index (WOMAC) score between revision strategies at 18 months, we calculated that a sample of 148 patients would give 80% power, assuming a two-sided type I error of 5% and attrition of 13% (128 participants with a primary end point).

Patients
We recruited 140 patients between March 2015 and September 2018 at 15 secondary care orthopaedic units (11 in England, one in Wales and three in Sweden). Eligible patients were aged ≥ 18 years, had a clinical diagnosis of hip prosthetic joint infection and required treatment with single- or two-stage revision surgery.

Randomisation
Randomisation was independently conducted by the Bristol Randomised Trials Collaboration. Randomisation was by a secure remote third party via an internet-based application or by telephone. Randomisation could not be carried out on the day of surgery because of the need to order equipment and for logistical planning in advance of surgery, but it occurred as close to the time of surgery as possible (≤ 12 weeks).

Patients were randomly allocated in a 1 : 1 ratio to one of the intervention groups. Randomisation within blocks of randomly varying size (four or six) was stratified by hospital.

Interventions

Owing to the nature of the intervention and planning requirements, surgeons and patients were made aware of the assigned treatment shortly after the baseline assessment and randomisation had been carried out. Patients were assigned to either single- or two-stage revision surgery.

All other aspects of treatment (antibiotics, analgesia, investigations, implants, static or articulating spacers, surgical techniques and approach) were in accordance with the treating surgeon's usual practice and in line with local policies and procedures. Usual clinical care continued throughout the study follow-up period.

Outcomes

Research assessments were carried out preoperatively and every 3 months until 18 months post randomisation. Data were collected from patient questionnaires and clinical performance tests and extracted from medical records.

The primary outcome measure was the total WOMAC score measured at 18 months post randomisation. The proposed follow-up duration of 24 months was changed to allow more time for recruitment and a lower risk of attrition. Eighteen months was chosen as the timing of primary outcome as maximum recovery from all surgeries should have been achieved and further health improvements would have been unlikely. Secondary outcomes measured every 6 months between 6 and 18 months post randomisation included the Brief Pain Inventory short form, the Oxford Hip Score, the Hip Dysfunction and Osteoarthritis Outcome and the Hospital Anxiety and Depression Score. WOMAC score measured at each 3-month follow-up was also a secondary outcome.

Statistical analysis

The study was reported as per CONSORT (Consolidated Standard of Reporting Trials) guidelines and the analyses were performed according to the predefined analysis plan agreed with the Trial Steering Committee.

The main analysis was based on a two-level linear mixed model regressing the repeated measures of total WOMAC score on allocation group, assessment time and their interaction, with adjustment for hospital and baseline total WOMAC score. The difference in mean total WOMAC score at 18 months post randomisation between patients who received single-stage revision and those who received a two-stage revision (reference) was identified using linear combination of the treatment effect, time of assessment and their interaction (contrast). Further analyses were conducted with imputation using chained equations[99] and the following sensitivity analyses were conducted: imputation of missing primary outcome assessments; accommodation of the possible range of WOMAC scores; adjustment for further baseline variables; imputation plus adjustment; and restriction to centres where a majority of two-stage procedures did not use a CUMARS.

Results

A CONSORT flow diagram is shown in *Figure 15*. Of 186 patients eligible for inclusion in the trial, 65 were randomised to single-stage revision and 75 were randomised to two-stage revision. The baseline characteristics of participants in the randomised groups are shown in *Appendix 17*, *Table 13*, and these were balanced between the groups, except that patients in the single-stage group were more likely to be male, with ASA grade 1 or 2 and have received previous non-surgical infection management.
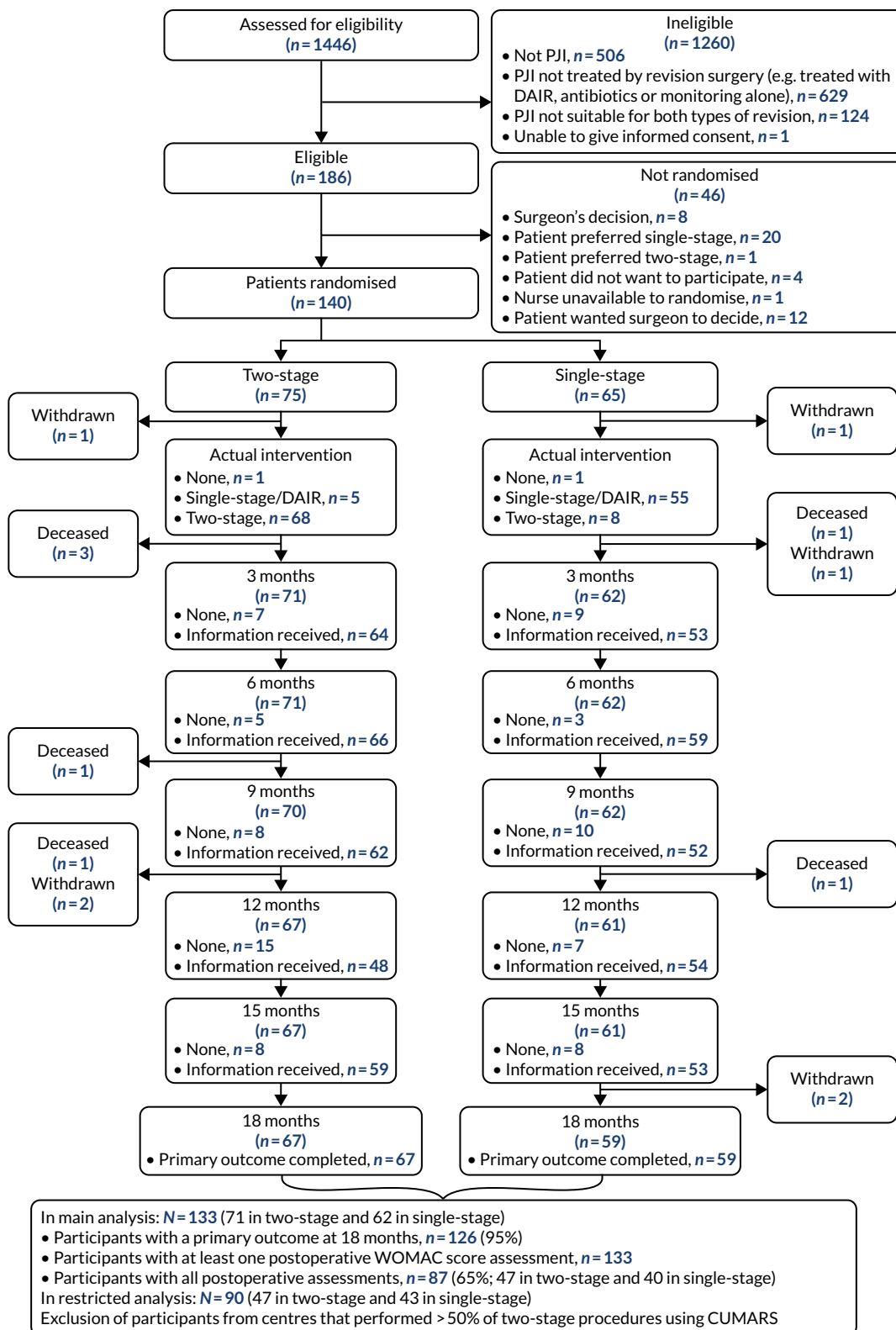
FIGURE 15 The INFORM RCT CONSORT flow diagram. PJI, prosthetic joint infection.

The groups were similar in the number and type of organisms cultured, the rates of culture-negative infection and the presence of a sinus tract. A total of 126 (90%) patients had the primary total WOMAC score outcome at 18 months post randomisation and 133 (95%) patients had at least one postoperative total WOMAC score and were included in the main analysis.

There was no evidence of a difference in the mean total WOMAC score at 18 months post randomisation between single- and two-stage management of hip prosthetic joint infection (mean difference favouring two-stage 0.13, 95% CI –8.20 to 8.46; $p = 0.98$) (*Figure 16*).

At 3 months post randomisation, participants in the single-stage procedure group had a better total WOMAC score (mean difference favouring single-stage 11.53, 95% CI 3.89 to 19.17; $p = 0.003$). This is greater than the minimal clinically important improvement of 7 (95% CI 4 to 10) reported by Bellamy *et al.*[100] in a before-and-after study in a general osteoarthritis population. Sensitivity analyses, with imputation of the 14 missing primary outcome assessments and accommodation of the possible range of WOMAC scores, adjusted for further baseline variables and imputation plus adjustment, and limited to centres where a majority of two-stage procedures did not use a CUMARS, supported the conclusions of the main analysis.

From 6 months post randomisation onwards, no difference was found between the two surgical procedures. Similar findings were found for all patient outcomes.

A higher rate of complications of surgery was seen among patients receiving a two-stage revision than among those receiving a single-stage revision (57.3% vs. 41.5%; $p = 0.04$) and this difference was marked for intraoperative events (26.7% vs. 7.7%; $p = 0.01$), predominantly calcar cracks and femoral shaft fractures (18 vs. 3). There was no evidence of a difference between the groups in length of hospital stay; other complications; rehospitalisation or reoperation due to prosthetic joint infection, the surgery or another cause; or serious adverse events or deaths (5 vs. 2). At 15–18 months post randomisation, 9 out of 59 (15%) patients who received single-stage revision had signs of infection in the operated hip, compared with 8 out of 67 (12%) who received two-stage revision ($p = 0.59$).
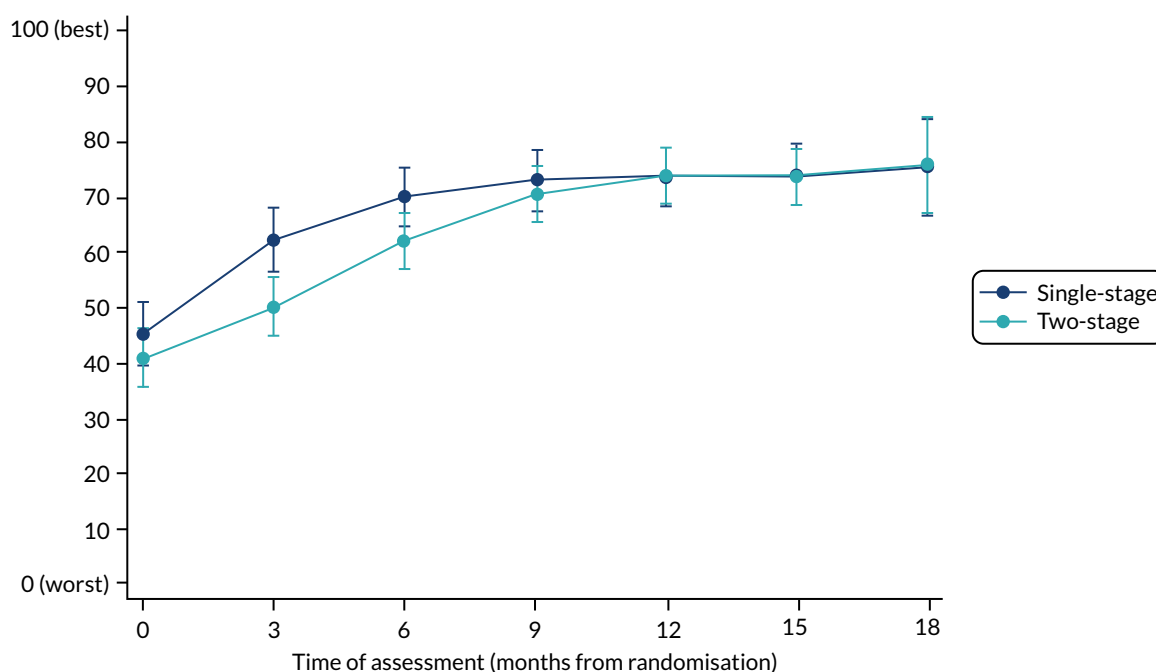
FIGURE 16 Mean (95% CI) global WOMAC score by revision surgery for prosthetic hip infection groups. A linear mixed regression model adjusted for place of surgery and accounting for participant repeated measures was used to produce the mean score at each time point.

Conclusion

As shown by the similarity in WOMAC total scores at 18 months after randomisation, the INFORM trial demonstrated that single- and two-stage revision are equally efficacious in the treatment of hip prosthetic joint infection. There was, however, an early improvement in WOMAC total scores in the single- compared with the two-stage group, which was clinically important. Given that patients state a strong preference for a quick return to normal activity, this should be considered when selecting the intervention. Further research should explore the value of earlier improvement to patients and health care. Single-stage surgery accounted for 30% of revision procedures for the treatment of prosthetic joint infection in 2014, so there is scope for increased utilisation.

Limitations

The INFORM study was powered for a patient-reported outcome and the sample size precluded study of infection clearance. The numbers of patients in the sensitivity analysis were large, except those restricted to centres where a majority of two-stage procedures did not use a CUMARS, which was limited to 90 patients.

Surgical treatment of prosthetic joint infection: the INFORM randomised controlled trial health economic analysis

Here we summarise the health economic analysis of the INFORM RCT described in *Appendix 18*.

Aim

To compare the cost-effectiveness of single- and two-stage revision surgery in the treatment of hip prosthetic joint infection.

Methods

The primary economic analysis was from an NHS and Personal Social Services (PSS) perspective, with a secondary analysis from a societal perspective. Resource use data relating to the initial surgery and subsequent treatment for revision of hip prosthetic joint infection were collected by research staff at each hospital at 3, 6, 9, 12, 15 and 18 months post randomisation. Admissions for revision surgery were microcosted and valued using information from the finance department of a treating hospital and the NJR. All subsequent inpatient stays, day cases and outpatient procedures were allocated an appropriate HRG code. NHS reference costs were used to value these stays, subsequent outpatient appointments and emergency department attendances. A self-reported resource use questionnaire was posted to participants at 6, 12 and 18 months post randomisation to collect information relating to community-based health-care use, prescribed medications and emergency department attendances; PSS provision received; personal expenses, including travel and home changes; and time off work, usual activities and informal care. Resources were valued using 2018–19 UK reference costs.[101–103]

The economic evaluation outcome measure was the quality-adjusted life-year (QALY), derived from the EuroQol-5 Dimensions, five-level version (EQ-5D-5L) questionnaire at baseline and at 3, 6, 12 and 18 months post randomisation. These were converted to utility scores using the validated mapping function to the existing EuroQol-5 Dimensions, three-level version (EQ-5D-3L) societal UK utility tariffs.[104] Total QALYs were calculated by linear interpolation using the AUC approach, taking into account any deaths that occurred during the study period by allocating those who died a zero utility in the time periods following their death.[105] A 3.5% discount rate was applied to all costs and outcomes occurring after 1 year.

Multiple imputation by chained equations using predictive mean matching was used to address missing data. Simple imputation methods assuming zero resource use in a returned participant questionnaire when no responses were given for an item, and using mean imputation where a participant had indicated the use of a resource but did not provide further details, were used prior to multiple imputation. Missing values for baseline utility were also imputed using the mean baseline utility value[106] prior to multiple imputation. The covariates in the imputation model were baseline utility, trial group, age, sex, ethnicity, education status, work status, hospital, ASA grade at first revision surgery and the latest surgical treatment for the management of prosthetic joint infection prior to study participation. Rubin's rules were used to combine the 62 individual imputations, and a randomisation seed was used to enable reproducible imputations.[99]

The adjusted mean costs and QALYs by trial group, the differences in adjusted mean costs and QALYs and the incremental net monetary benefit (iNMB) were estimated using the seemingly unrelated

regression method, which accounts for the correlation between costs and QALYs.[107] Costs and QALYs were adjusted for study centre. QALYs were also adjusted for baseline utility. National Institute for Health and Care Excellence (NICE) willingness-to-pay thresholds of £20,000 and £30,000 per QALY were used. Sample uncertainty within the cost-effectiveness estimates was explored using cost-effectiveness acceptability curves (CEACs) derived from the estimates of the seemingly unrelated regression. Sensitivity analyses (see *Appendix 18*, *Table 20*) were undertaken to account for uncertainty in the parameters used in the cost-effectiveness analyses.

Results

Owing to differences in the collection of resource use data for UK and Swedish participants, the primary economic analysis was conducted on 128 participants from England and Wales using a multiply imputed data set.

Total theatre time was longer for those randomised to two-stage revision, and these patients spent longer in intensive care and recovery and had a longer overall hospital stay. They also had a greater number of subsequent inpatient stays and emergency department attendances. There were a greater number of primary care practice nurse visits for those randomised to a single-stage procedure, whereas those randomised to a two-stage procedure had a greater number of district nurse home visits, stays in residential homes and home care worker visits.

The EQ-5D-5L utility values at all time points are shown in *Table 5*. These illustrate the different pathways of the two procedures, with patients randomised to the single-stage procedure seeing a gradual improvement in their utility values from 3 months onwards, whereas for those randomised to the two-stage procedure the improvement begins only at 6 months.

Table 6 shows that the mean costs from the treating hospital were higher in the first year of follow-up in the single-stage group; however, in the last 6 months of the trial these costs were similar in the trial groups, indicating that the trial follow-up is sufficiently long to capture differences in costs.

The total adjusted mean costs in the single-stage group (£36,256) from the NHS/PSS perspective were lower than in the two-stage group (£46,312), a cost difference of −£10,055 (95% CI −£19,568 to −£542). The cost difference reduced slightly from the societal perspective (−£9450, 95% CI −£22,855 to £3956). Participants in the single-stage group had a greater number of adjusted mean QALYs (0.75) than those in the two-stage group (0.69), a difference of 0.06 (95% CI −0.07 to 0.18).

TABLE 5 Mean unadjusted (95% CI) EQ-5D-5L utility value by time point and randomised allocation[a]

Time point	Single-stage revision surgery		Two-stage revision surgery	
	n	Mean utility (95% CI)	*n*	Mean utility (95% CI)
Baseline	60	0.32 (0.23 to 0.41)	67	0.28 (0.20 to 0.36)
3 months	50	0.51 (0.41 to 0.61)	62	0.33 (0.23 to 0.42)
6 months	45	0.54 (0.44 to 0.64)	56	0.46 (0.37 to 0.55)
12 months	49	0.54 (0.44 to 0.64)	56	0.50 (0.42 to 0.59)
18 months	52	0.60 (0.50 to 0.70)	60	0.60 (0.52 to 0.68)

a With the exception of baseline utility (missing values imputed using mean baseline utility scores), complete-case values are given.

TABLE 6 Mean unadjusted treating hospital surgical admissions and follow-up by time period and randomised allocation[a]

	Single-stage revision surgery		Two-stage revision surgery	
	n	Mean cost (£) (95% CI)	*n*	Mean cost (£) (95% CI)
Surgical admissions (0–6 months)	58	21,287 (18,250 to 24,323)	62	25,674 (21,696 to 29,652)
Follow-up outpatient visits and admissions (0–6 months)	56	894 (123 to 1664)	63	820 (427 to 1213)
Surgical admissions (6–12 months)	58	2039 (613 to 3466)	62	3660 (1688 to 5632)
Follow-up outpatient visits and admissions (6–12 months)	56	437 (72 to 802)	63	444 (181 to 707)
Surgical admissions (12–18 months)	58	1593 (–426 to 3612)	62	1489 (–76 to 3055)
Follow-up outpatient visits and admissions (12–18 months)	56	484 (453 to 516)	63	702 (443 to 962)

a Complete-case values are given.

From the NHS/PSS perspective, the iNMB of single-stage revision compared with two-stage revision was £11,167 (95% CI £638 to £21,696) at £20,000 per QALY willingness-to-pay threshold, and at this threshold there was a 98% probability that the single-stage procedure was the cost-effective option. This reduced to 92% from the societal perspective. All sensitivity analyses conducted from the NHS/PSS perspective showed that the probability of the single-stage procedure being cost-effective was at least 98%.

Conclusion

The two hospital stays in a two-stage procedure led to the higher cost in this group. The EQ-5D-5L scores illustrate that while patients were waiting for their second-stage operation they had a poorer quality of life, which was reflected in the overall QALY score. The greater use of district nurse home visits and home care worker visits indicates that these patients were also less able to self-care and leave their home.

The within-trial economic evaluation has shown, with a great degree of certainty, that the single-stage procedure is the cost-effective option for patients with hip prosthetic joint infection.

Limitations

The analysis has limitations in relation to missing data, particularly for resource use as obtained from patient-completed questionnaires. A complete-case analysis could only be conducted from a treating hospital perspective, and indicated higher QALY values in both groups, indicating that those who did not complete all the questionnaires were likely to have poorer quality of life than those who did. Multiple imputation was used to account for the missing data, using data at each time point in the model, meaning that all available data were used. This meant that the multiple imputation could not be conducted by trial group. However, sensitivity analyses on different specifications of the multiple imputation model indicate that the model specification is unlikely to have affected the conclusions of the analysis.

Cost differences may extend beyond the 18-month trial follow-up. However, the randomised groups had similar hospital-based costs accruing between 12 and 18 months' follow-up and had similar mean WOMAC and EQ-5D-5L scores at 18 months. There was also little to suggest a difference in reinfection rates between groups. Together, these suggest that patient outcomes and hospital costs may not differ in the longer term.

Surgeons' views on the acceptability of trial information and recruitment

Aims

We aimed to explore surgeons' experience and acceptance of the randomisation process, their understanding of equipoise, and their views on information about the trial and interventions.

Methods

We conducted telephone interviews with 12 surgeons from eight sites participating in the trial. We used a topic guide developed in collaboration with INFORM surgeons. Topics included surgeons' experiences and acceptability of the randomisation process and their views on surgical equipoise, and information about the trial and interventions. Data were analysed using a descriptive qualitative approach and reported to the trial management group to inform the recruitment process and identify areas for improvement.

Results

Surgeons were happy with the information they received about the trial and the randomisation process. We identified a number of potential barriers to recruitment and areas for improvement. The complexity of cases often precluded patients from randomisation, and often this was because the surgeon lacked equipoise in that particular case. Some surgeons suggested that there was a lack of engagement at their centres and that their colleagues lacked equipoise about the trial. Recruitment of patients was difficult as prosthetic joint infection is a rare condition and we did not have the resources and staff to find eligible patients opportunistically at routine outpatient or emergency appointments. At one centre, a change in referral patterns meant that the number of patients being referred had reduced. We addressed these barriers in the following ways:

- We originally planned to recruit patients from four centres but increased this number in the early stages of the trial when we realised that recruitment would be a challenge. The funding of additional sites was met from the existing budget and with UK Clinical Research Network portfolio support.
- We continued to collect data on patients deemed ineligible.
- We communicated anonymised case studies from two recruiting centres to surgeons in the other centres to demonstrate the range of patients randomised and the characteristics of individual cases. This resulted in debate and dialogue between surgeons regarding equipoise.
- We communicated directly with all surgeons operating on patients with prosthetic joint infection within collaborating trusts to ensure that they remained engaged.
- We communicated findings of other work packages to surgeons through newsletters to enhance understanding of the broad context of INFORM.
- We held workshops with recruiting nurses to provide them with training and support on ways to identify and recruit patients and to ensure that potential participants were brought to the attention of participating surgeons.
- The chief investigator and the clinical lead of work package 4 hosted information events at national conferences and visited collaborating centres to explore local service and recruitment pathways to ensure that eligible patients were identified and that surgeons remained engaged.

Conclusion

Data from interviews with surgeons in the early phase of the trial enabled us to identify barriers to recruitment and implement remedial strategies to improve recruitment.

Surgical treatment of prosthetic joint infection: patient experience of treatments in the INFORM randomised controlled trial

Here we summarise our published article.[108]

Aims

We aimed to explore the early and long-term experiences of patients receiving single- and two-stage revision. In patients with two-stage revision we also aimed to explore experiences of patients with either a temporary cement spacer or CUMARS.

Methods

On two occasions, we interviewed 32 people participating in the INFORM RCT who had received single- or two-stage revision surgery for hip prosthetic joint infection. Patients were interviewed at 2–4 months and 18 months after their first revision operation.

Interview topic guides were developed with the INFORM PPI group but were flexible to allow participants to discuss areas that they felt were important. Themes were generated from the data inductively using the constant comparative method.

Results

Thirty people were interviewed 2–4 months after their first revision operation, and 17 were interviewed at the 18-month follow-up. The overall sample of 32 patients comprised 15 women and 17 men and had a mean age of 68.9 years (range 51 to 89 years). Eleven had received a single-stage and 21 had received a two-stage revision. Of those who had received a two-stage revision, seven had a cement spacer, 10 had a CUMARS and four had an excised hip with no spacer.

During their early recovery period, people who had received single- or two-stage revision for hip prosthetic joint infection experienced prolonged hospital stays of 2–4 weeks, difficult antibiotic regimens and only brief physiotherapy. People described the practical challenges and gains that they had experienced during day-to-day life while recovering from revision at home and identified their needs for information and support during recovery. At 18 months post revision, all patients described improvements in mobility and independence, but they also reported ongoing restrictions to walking and some functional limitations. People also described their emotional resilience and benefits from participating in the INFORM RCT.

The experiences of people who received a two-stage revision with a cement spacer or excised hip differed from those receiving single-stage revision or a two-stage revision with a CUMARS. Patients who received a single-stage revision or a two-stage revision with a CUMARS had greater mobility and independence in the early stages of recovery. However, patients who received a cement spacer or CUMARS perceived that their recovery was slow, and those with a CUMARS reported dislocations and uncertainty about the need for further surgery.

Conclusion

After treatment for prosthetic joint infection, important aspects of patient recovery relate to mobility, function, pain and independence. Patients who receive single- and two-stage revision experience different patterns of recovery and these are also influenced by use of a spacer and CUMARS. To be supported during treatment and recovery, patients require appropriate information and opportunities to talk and share experiences.

Limitations

The comparison of experiences of recovery at both the postoperative and the 18-month time points in the same patients was limited as we were not able to reinterview all 30 of the original participants. We interviewed other participants at 18 months to balance the characteristics of the sample and to ensure saturation. The participants who took part in the qualitative study may have been those who were most positive about trial participation.

Patient preferences for revision surgery after prosthetic joint infection

Here we summarise our published article.[109]

Aims

Single- and two-stage revision options for treatment of prosthetic joint infection each have implications for the patient time course and experience of recovery. We aimed to assess the surgical preferences of patients who had received revision surgery for hip prosthetic joint infection.

Methods

We undertook a discrete choice experiment to quantify the surgical preferences of patients who had received a single- or two-stage revision for hip prosthetic joint infection. In a discrete choice experiment, participants choose between features of interventions or approaches to care. These are attributes that can have different levels. A checklist based on the guidance of Lancsar and Louviere[110] is provided in *Appendix 19*.

Attributes

Attributes were developed from our INFORM qualitative patient interviews into the impact of hip prosthetic joint infection and revision surgery described in *Patients' experiences of prosthetic joint infection after hip or knee replacement and its treatment.*[57] These data were analysed thematically, and attributes and levels were assigned.[111] We identified four attributes of revision surgery for hip prosthetic joint infection and defined levels (*Table 7*). Pairs of profiles were designed using a moduloarithmetic process, ensuring full balance and efficiency in the design.[112] To create a manageable questionnaire, the 32 feasible pairs of profiles were reduced to 16 using an orthogonal main effects plan to produce a fractional factorial design for the final questionnaire (see *Appendix 20*). The questionnaire was piloted and refined in collaboration with five PPI representatives.

TABLE 7 Discrete choice experiment attributes and levels

Attribute	Levels
Number of operations	One operation
	Two operations
Ability to engage in valued activities after new hip is fitted	Can do everything
	Can do most things
	Cannot do most things
	Cannot do anything
Time taken after surgical treatment starts to return to normal activities (months)	3
	6
	12
	18
Antibiotic side effects	Affect me a lot
	Do not affect me much

Sample size

Recognising the rarity of hip prosthetic joint infection, a sample size of ≥ 50 patients was considered appropriate.

Participants

Patients recruited to the INFORM RCT were invited to complete the questionnaire at their 18-month follow-up. The questionnaire was posted to participants for self-completion or completed with the assistance of a research nurse during a hospital clinic visit.

Data analysis

Questionnaire data were effects-coded[113] and analysed using Stata SE version 15 (StataCorp LP, College Station, TX, USA). The influence of the four attributes on patient choices was analysed using a conditional logit model (pseudo $R^2 = 0.182$). The effect-coding of attribute levels gives a mean coefficient of zero across each attribute.

Results

Questionnaires were sent to 80 patients at nine orthopaedic centres, and 57 were fully completed (71%). The mean age of patients was 70 years (range 51–90 years); 21 (37%) were female, 26 (46%) had received single-stage revision, 14 (25%) lived alone and 41 (72%) were retired. The questionnaire took between 20 and 40 minutes to complete.

Regression coefficients and results are shown in *Table 8*. Participants had the strongest preference for a surgical option that resulted in the least restrictions on engagement in valued activities after the new hip was fitted, illustrated by the largest preference weight. Less valued but important preferences were

TABLE 8 Discrete choice task results from conditional logistic regression

Attribute	Coefficient	SE	95% CI	*p*-value
Ability to engage in valued activities after new hip is fitted				
Can do everything[a]	0.70			
Can do most things	0.49	0.08	0.33 to 0.64	< 0.001
Cannot do most things	−0.39	0.07	−0.53 to −0.24	< 0.001
Cannot do anything	−0.80	0.13	−1.05 to −0.55	< 0.001
Antibiotic side effects				
Do not affect me much[a]	0.22			
Affect me a lot	−0.22	0.05	−0.33 to −0.12	< 0.001
Number of operations				
1[a]	0.20			
2	−0.20	0.07	−0.35 to −0.06	< 0.001
Time taken after surgical treatment starts to return to normal activities (months)				
3[a]	0.20			
6	0.31	0.09	0.14 to 0.48	< 0.001
12	−0.06	0.05	−0.15 to 0.04	0.22
18	−0.45	0.10	−0.64 to −0.26	< 0.001

SE, standard error.
a Reference category within attribute.

for a surgical treatment that would result in a shorter time to return to normal activities, few or no side effects from antibiotics, and only one operation. The results also suggest that the least restrictions on engaging in valued activities and the shortest time taken to return to normal activity are the individual attributes most valued by patients. This is indicated by the larger spread of coefficients. The most acceptable option was a time period of between 3 and 6 months to return to normal activity. There was no clear preference up to 12 months, but 18 months was considered unacceptable.

Conclusion

The most valued factors 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.

Limitations

Feedback from early participants suggested that completing the questionnaire was difficult. However, after the instructions and format were altered and when nurse support was provided, participants were able to understand and complete the questionnaire. Our chosen analysis method of conditional logistic regression assumes preference homogeneity and it may be that participants exhibit a level of heterogeneity that cannot be captured using this method. The use of latent class analysis could further explore the patterns in choice data that suggest preference heterogeneity, but our sample size was too small for these explorations to be conducted.

Dissemination of the INFORM programme

Dissemination of our results has been extensive. Some activities have been more limited than planned owing to the COVID-19 pandemic. However, it is our intention to pursue activities further when group gatherings are permitted.

Publications

All our research is published or submitted, or analyses are in progress. Several articles have become highly cited in their area, including those relating to risk factors, the patient experience, diagnostic tests and treatments.

British Hip Society

The significance of the INFORM programme is recognised by the British Hip Society and an afternoon symposium was given over to presentation and discussion of results at the 2020 annual meeting in South Wales (see *Appendix 21*).

International Consensus Meeting on Periprosthetic Joint Infection

To address the wide international variation in prevention and treatment of prosthetic joint infection, the International Consensus Meeting on Periprosthetic Joint Infection was organised by Thorsten Gehrke and Javad Parvizi. The meeting took place in July 2018 and the INFORM programme was represented by Setor Kunutsor.

Conferences

The results from the INFORM programme have been presented at European Federation of National Associations of Orthopaedics and Traumatology (EFORT), International Society of Arthroplasty Registries (ISAR), European Orthopaedic Research Society (EORS), British Sociological Association (BSA), Combined Orthopaedic Associations (COMOC), British Pain Society (BPS), British Society for Rheumatology (BSR), British Orthopaedic Association (BOA) and British Hip Society (BHS) conferences.

M Shed

A 1-day conference was planned for May 2020 to present results to patient-partners, INFORM trial participants and representatives of recruitment centres. This will be rescheduled when feasible.

Implications of the INFORM programme

Overview

In the INFORM programme, we critically reviewed existing research and conducted new high-quality studies with the aim of improving treatment and outcomes for people with hip and knee prosthetic joint infection. Work packages either informed each other or triangulated results. Our studies were supported with extensive PPI.

Our NJR analyses showed that, in the UK, rates of revision surgery within 10 years of primary hip and knee replacement are 0.62% and 0.75%, respectively, but are about four times higher after aseptic revision. Further NJR analyses and meta-analyses of previous research identified multiple modifiable and non-modifiable patient and surgical risk factors, potentially allowing for better counselling of patients and the suggestion of preventative strategies.

Qualitative studies highlighted that infection and revision treatments have a devastating and long-lasting impact on patients and their families, who report that more psychosocial support is required to address unmet needs. Patients and surgeons described prolonged treatments and periods of uncertainty. Important attributes of a patient being considered for revision surgery for hip prosthetic joint infection were identified. In surgeon interviews specifically focusing on the INFORM trial, barriers to recruitment were identified and remedial strategies implemented.

The use of DAIR is effective in > 60% of cases and is more efficacious if performed early. Surgeons should be encouraged to act promptly when infection has occurred.

The INFORM randomised trial shows that revision for hip prosthetic joint infection is equally efficacious with a single- and a two-stage procedure, and good long-term patient outcomes are achieved in a wide range of patients. Two-stage revision is the more widely used treatment, but the use of single-stage revision has increased, with about 30% of revisions for hip and 19% for knee prosthetic joint infection having been performed in single operations in 2014. Single-stage revision gives better patient-reported outcomes in the first 3 months, but not thereafter.

In the INFORM trial, single-stage surgery was cost-effective in terms of QALYs compared with two-stage surgery for treatment of hip prosthetic joint infection, but infection is very expensive to treat.

Any greater risk of reinfection or new infection after a single-stage procedure than after a two-stage procedure seen in NJR analyses may be limited to the first few months after surgery. In this period, patients receiving a two-stage revision may also have infections that have not fully cleared, leading to delay in the second stage reimplantation. Thus, as with a two-stage revision, close monitoring of patients with a single-stage revision is warranted. Patients with a single-stage revision for treatment of hip prosthetic joint infection have a smaller number of operations overall. In meta-analysis and IPD meta-analysis, the single-stage revision strategy for hip prosthetic joint infection is a reasonable option with acceptable rates of infection control. Reinfection rates after single- and two-stage revision for knee prosthetic joint infection were similar and those patients receiving single-stage revision received considerably fewer operations.

Complementing the results of the INFORM trial, responses to the discrete choice experiment suggested that patients identify the ability to engage in valued activities and the time taken to return to normal activity as the most valued characteristics in decisions about revision surgery. Other preferences are

less severe side effects from antibiotics and revision with only one operation. Recognising the different outcome trajectories of single- and two-stage revision, the choice of intervention should be based on the patient's preference for the recovery profile that is important to them.

Limitations

Our research studies have limitations that may affect their generalisability.

General

- Our studies mainly included people with joint replacement for osteoarthritis and the results may not be generalisable to other indications.
- Some research was specific to people with hip prosthetic joint infection.

National Joint Registry and systematic reviews

- Study populations may have been selected for specific treatments based on their health status and infecting organism.
- In NJR studies, 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 non-surgically.
- With observational data, we cannot establish for certain whether or not relationships between risk factors and revision for prosthetic joint infection are causal.
- Individual patient data meta-analysis was limited by a lack of available data for some clinically relevant subgroups.
- Few studies were identified reporting outcomes after single-stage revision for knee prosthetic joint infection.
- Few studies collected patient-reported outcomes.

Randomised trial

- The INFORM trial was not powered to study reinfection and was limited to 18 months' follow-up.
- Some centres used a CUMARS in the first stage of a two-stage revision, with the option of leaving in situ permanently.

Qualitative studies

- Subgroups were small.
- Patients reporting experiences of revision strategies may have been those most positive about trial participation.

Health economic studies

- The resources included in cost calculations in the studies we reviewed varied considerably.
- In NJR analyses, we did not consider costs relating to outpatient, primary and community care, prescribed medications and treatments received outside England.
- In the INFORM trial, there were substantial missing data relating to resource use.

Review of diagnostic tests

- There was an exclusive focus on two promising biomarkers.
- A majority of studies of alpha defensin were conducted by a research group holding patents for related products.

Discrete choice questionnaire

- Sample size limited options for analysis and was too small to allow an exploration of responses in different subgroups.

Research recommendations

- In collaboration with patients and health-care professionals, develop clear information for people receiving treatments for prosthetic joint infection.
- Develop, implement and evaluate enhanced care pathways for people with hip and knee 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 lead to earlier recognition of signs and symptoms of infections.
- Future work could look at preparedness for adverse outcomes, help-seeking in impactful situations, and information for health-care professionals about early signs and care for prosthetic joint infection.
- Develop targeted preventative strategies for high-risk patients, for example better control of comorbidities such as diabetes and effective weight loss strategies in patients with very high BMI.
- Explore the effectiveness of counselling, monitoring and targeted preventative strategies based on risk factors for prosthetic joint infection.
- Use of the CUMARS has increased and research into their long-term survival is required.
- The role of spacers in two-stage revisions needs to be appraised in view of the high prevalence of complications associated with their use.
- The relative efficacy and cost-effectiveness of single- compared with two-stage revision surgery should be explored in certain high-risk subgroups, in particular those with difficult-to-treat organisms and culture-negative infections.
- The use of a single-stage revision strategy in knee prosthetic joint infection has increased and a randomised evaluation is needed.
- Further independent comparisons in UK representative cohorts should be made between synovial fluid alpha-defensin and leucocyte esterase, and traditional diagnostic tests to assess their relative clinical effectiveness and cost-effectiveness.
- The majority of the minor criteria in the MSIS diagnostic criteria for prosthetic joint infection are not routinely available or used in the diagnosis of prosthetic joint infection in the NHS setting, and a set of diagnostic criteria relevant to contemporary NHS practice needs to be established and assessed.

Reflections on work packages

The involvement of our PPI group was valuable in all work packages. The group gave support to the INFORM RCT, which helped with the recruitment, retention and engagement of patients. The model of taking research to the patients was welcomed by patients, who found that inviting clinicians and researchers to meetings 'owned' and run by the PPI group was preferable to and less intimidating than patients attending research and management meetings. Patients felt happy to set the agenda and direct the meetings over which they had ownership. Researchers and clinicians found this refreshing and informative.

Members of the INFORM group carrying out secondary research felt that discussing the methods and results of the evidence synthesis with the PPI group helped them appreciate the significance of prosthetic joint infection and its treatment to patients. In the field of prosthetic joint infection,

systematic reviews included many published studies that had small sample sizes. There is a need for more collaborative analyses. Investigators were very willing to share data for the IPD meta-analysis and we wish that we had done more IPD analysis on related topics. Further work using this approach is planned. Hopefully, in future, there will be more data from clinical trials that will benefit from meta-analysis.

Something that stands out is the value of the qualitative work in giving a small patient population a voice. The work was very important in the programme and we wish that we had done more qualitative work to further understand the experience of patients, their significant others and health-care workers treating infection. Although prosthetic joint infection affects only a small proportion of patients who undergo joint replacement, our work has shown just how devastating and life-changing its impact can be and has identified an important need for further supportive care pathways. It has also given surgeons a voice. While prosthetic joint infection has been identified as every orthopaedic surgeon's 'worst nightmare',[62] until now its impact on surgeons' professional and personal well-being had not been addressed in the literature. We hope that this work in some ways helps surgeons to broach the topic with colleagues in a supportive fashion, rather than, as one surgeon suggested, 'burying your head in the sand'.

Across all study designs, the significance of patient outcomes and not just reinfection was reinforced in interviews with patients and surgeons and meetings with the PPI group.

We enjoyed undertaking a discrete choice experiment in orthopaedics, even though it proved challenging for patients and, ultimately, quite labour intensive. The results gave novel insights into what was important to patients. In future studies, we will undertake training and methodological work to make this research easier for participants.

The NJR proved a rich resource for exploring the significance of prosthetic joint infection to the NHS. The sheer number and breadth of data afforded by NJR/HES linkage allowed an exploration of secular trends, risk factors and treatments that is not possible with other observational data sets. We are encouraged to see the establishment and development in the UK of similar large national audits for other conditions.

To guide decisions on appropriate care, the top level of evidence in the hierarchy of primary research is the RCT, which is acknowledged to be difficult when comparing surgical procedures. The INFORM multicentre trial was completed successfully and showed that equipoise and random allocation of treatments for prosthetic joint infection was acceptable to patients and surgeons. The trial was a difficult undertaking. For anyone replicating it, we recommend opening many sites early, spending time encouraging surgeons, and getting surgeons at different centres to talk to each other about cases to set their minds at ease. The use of a per-patient fee at research centres was critical in a trial focusing on a rare condition.

Challenges and successes

Having been involved in a number of NIHR Programme Grants, we are particularly pleased with the large volume of clear results of direct relevance to patients, clinicians and health-care providers that this programme has delivered. We now have new important knowledge on impact, risk factors and treatment that will inform care.

The qualitative work, PPI and evidence synthesis were particularly productive. The IPD analysis allowed us to internationalise the programme and it was pleasing to have such willing international co-operation leading to an important scientific publication. The evidence synthesis could, therefore, expand beyond the original aims and cover infection in a large range of joints.

Despite our extensive experience with NJR/HES, this work was initially more complex than we had anticipated, with lengthy data cleaning and the careful unpicking of the complex patient journey.

For example, many patients do not simply received a single- or two-stage revision but have multiple first stages before the second stage. Despite this, the work package delivered excellent outputs, which are already influencing care and are highly cited.

Certainly, the most challenging aspect of the study was the randomised trial. Possibly quite predictably, we overestimated recruitment rates at some centres and had to open more centres than initially planned. This necessitated extending the programme to 6 years. Costs, however, were contained by introducing a per-patient fee with payments tied to milestones. We would encourage researchers to adopt this funding model, which incentivises centres and controls costs. It may be argued that a RCT focusing on the treatment of infection should be powered to study infection clearance. Our previous research, patient interviews and PPI indicated that patients, rather than being concerned with biomedical outcomes relating to prosthesis survival and further treatments, are concerned about pain, function and well-being after surgery. When data accrue from further RCTs, meta-analysis will allow a more thorough analysis of infection clearance after single- and two-stage revision.

In the programme, it was excellent to be able to approach important questions using a variety of methods and resources. When answers concurred, this was very reassuring.

Service developments

We have shown that infection is devastating and that patients lack the physical and psychological support that they have identified as necessary. We have identified the patients at highest risk, allowing adequate preoperative counselling and targeted measures to decease risks. We have delineated the efficacy of DAIR and shown that early intervention markedly improves the success rate of this treatment. Single- and two-stage revision appear equally efficacious, and both achieve good results; however, single-stage surgery gives better early results and is cost-effective in terms of QALYs. Surgeons can, therefore, feel confident to adopt this treatment.

Acknowledgements

W̶e would like to thank all the patients, surgeons, health-care professionals, patient partners and researchers who have contributed to the INFORM programme. We acknowledge support from the NIHR Clinical Research Network.

Trial Steering Committee

We thank the members of the Trial Steering Committee for their support in the development, conduct and delivery of the INFORM RCT:

- Professor Rod Taylor, University of Exeter
- Martyn L Porter, Centre for Hip Surgery, Wrightington Hospital
- Ali Heawood, Bristol Medical School: Population Health Sciences
- Julie Chappell, DAC Beachcroft, Bristol.

INFORM group

The INFORM group comprises the following.

Lead surgeons recruiting patients to INFORM studies
Richard Baker, Tim Board, Ben Burston, Pedro Foguet, Ed Gardner, Peter Grant, Stephen Jones, Sanchit Mehendale, Jonathan Miles, Michael C Parry, Andrew J Porteous, Mike Reed, Jörg Schilcher, Olof Sköldenberg, Ian Stockley, Karin Svensson, Adrian H Taylor, Andrew D Toms, Jason CJ Webb, J Mark Wilkinson and Matthew J Wilson.

Study co-ordinator for centres in Sweden
Lotta Falkendahl.

Collaborators with specific expertise
Matthew C Barrett, Richard S Craig, Elizabeth Darley, Paul Dieppe, Tim J Peters, Caoimhe Rice, Michael C Wyatt and Vikki Wylde.

Patient partners
Edith Anderson, Lizzy Betts, Charlie Brimble, Pat Clark, Debby Collett, Sue Comley, Vernon Cooper, Geoff Dyer, Enid Edwards, Ken Kent, Mike Nicholson, David Peacock, Sheila Spence and Jean Welham-Clarke.

Support for recruitment, data collection and administration
Marie Burgess, Beverley Evanson, Louise Hawkins, Kristina Lewis and Makita Werrett.

Contributions of authors

Ashley W Blom (https://orcid.org/0000-0002-9940-1095) (Professor of Orthopaedic Surgery) was chief investigator with responsibility for the delivery of the overall programme and lead for work package 4. He is the corresponding author.

Publications

Kunutsor SK, Whitehouse MR, Blom AW, Beswick AD, INFORM Team. Re-infection outcomes following one- and two-stage surgical revision of infected hip prosthesis: a systematic review and meta-analysis. *PLOS ONE* 2015;**10**:e0139166. https://doi.org/10.1371/journal.pone.0139166

Kunutsor SK, Whitehouse MR, Webb J, Toms A, Stockley I, Taylor A, *et al.* Re-infection outcomes following one- and two-stage surgical revision of infected hip prosthesis in unselected patients: protocol for a systematic review and an individual participant data meta-analysis. *Syst Rev* 2015;**4**:58. https://doi.org/10.1186/s13643-015-0044-0

Moore AJ, Blom AW, Whitehouse MR, Gooberman-Hill R. Deep prosthetic joint infection: a qualitative study of the impact on patients and their experiences of revision surgery. *BMJ Open* 2015;**5**:e009495. https://doi.org/10.1136/bmjopen-2015-009495

Kunutsor SK, Whitehouse MR, Blom AW, Beswick AD, INFORM Team. Patient-related risk factors for periprosthetic joint infection after total joint arthroplasty: a systematic review and meta-analysis. *PLOS ONE* 2016;**11**:e0150866. https://doi.org/10.1371/journal.pone.0150866

Kunutsor SK, Whitehouse MR, Lenguerrand E, Blom AW, Beswick AD, INFORM Team. Re-infection outcomes following one- and two-stage surgical revision of infected knee prosthesis: a systematic review and meta-analysis. *PLOS ONE* 2016;**11**:e0151537. https://doi.org/10.1371/journal.pone.0151537

Strange S, Whitehouse MR, Beswick AD, Board T, Burston A, Burston B, *et al.* One-stage or two-stage revision surgery for prosthetic hip joint infection – the INFORM trial: a study protocol for a randomised controlled trial. *Trials* 2016;**17**:90. https://doi.org/10.1186/s13063-016-1213-8

Wyatt MC, Beswick AD, Kunutsor SK, Wilson MJ, Whitehouse MR, Blom AW. The alpha-defensin immunoassay and leucocyte esterase colormetric strip test as diagnostic tests in periprosthetic infection: a systematic review and meta-analysis. *J Bone Joint Surg Am* 2016;**98**:992–1000. https://doi.org/10.2106/JBJS.15.01142

Kunutsor SK, Beswick AD, Peters TJ, Gooberman-Hill R, Whitehouse MR, Blom AW, Moore AJ. Health care needs and support for patients undergoing treatment for prosthetic joint infection following hip or knee arthroplasty: a systematic review. *PLOS ONE* 2017;**12**:e0169068. https://doi.org/10.1371/journal.pone.0169068

Kunutsor SK, Whitehouse MR, Blom AW, Beswick AD. Systematic review of risk prediction scores for surgical site infection or periprosthetic joint infection following joint arthroplasty. *Epidemiol Infect* 2017;**145**:1738–49. https://doi.org/10.1017/S0950268817000486

Lenguerrand E, Whitehouse MR, Beswick AD, Jones SA, Porter ML, Blom AW. Revision for prosthetic joint infection following hip arthroplasty: evidence from the National Joint Registry. *Bone Joint Res* 2017;**6**:391–8. https://doi.org/10.1302/2046-3758.66.BJR-2017-0003.R1

Lenguerrand E, Whitehouse MR, Beswick AD, Toms AD, Porter ML, Blom AW, National Joint Registry for England, Wales, Northern Ireland and the Isle of Man. Description of the rates, trends and surgical burden associated with revision for prosthetic joint infection following primary and revision knee replacements in England and Wales: an analysis of the National Joint Registry for England, Wales, Northern Ireland and the Isle of Man. *BMJ Open* 2017;**7**:e014056. https://doi.org/10.1136/bmjopen-2016-014056

Garfield K, Noble S, Lenguerrand E, Whitehouse MR, Sayers A, Reed MR, Blom AW. What are the inpatient and day case costs following primary total hip replacement of patients treated for prosthetic joint infection: a matched cohort study using linked data from the National Joint Registry and Hospital Episode Statistics. *BMC Med* 2020;**18**:335. https://doi.org/10.1186/s12916-020-01803-7

Kunutsor SK, Barrett MC, Whitehouse MR, Blom AW. Clinical effectiveness of treatment strategies for prosthetic joint infection following total ankle replacement: a systematic review and meta-analysis. *J Foot Ankle Surg* 2020;**59**:367–72. https://doi.org/10.1053/j.jfas.2019.04.016

Kunutsor SK, Barrett MC, Whitehouse MR, Craig RS, Lenguerrand E, Beswick AD, Blom AW. Incidence, temporal trends and potential risk factors for prosthetic joint infection after primary total shoulder and elbow replacement: systematic review and meta-analysis. *J Infect* 2020;**80**:426–36. https://doi.org/10.1016/j.jinf.2020.01.008

Palmer CK, Gooberman-Hill R, Blom AW, Whitehouse MR, Moore AJ. Post-surgery and recovery experiences following one- and two-stage revision for prosthetic joint infection – a qualitative study of patients' experiences. *PLOS ONE* 2020;**15**:e0237047. https://doi.org/10.1371/journal.pone.0237047

Blom AW, Lenguerrand E, Strange S, Noble SM, Beswick AD, Burston A, *et al.* Clinical and cost effectiveness of single stage compared with two stage revision for hip prosthetic joint infection (INFORM): pragmatic, parallel group, open label, randomised controlled trial. *BMJ* 2022;**379**:e071281.

INFORM conference presentations

Beswick A, Strange S, Whitehouse M, Blom A. *Prosthetic Joint Infection: The INFORM Programme.* EORS; Bristol, UK, September 2015.

Gooberman-Hill R, Moore A. *Impact and Preference for Treatment of Infection after Joint Replacement.* EORS; Bristol, UK, September 2015.

Kunutsor S, Whitehouse M, Blom A, Beswick A. *One- or Two-stage Surgical Revision of Infected Hip Prosthesis: A Meta-analysis.* EORS; Bristol, UK, September 2015.

Moore A, Blom A, Whitehouse M, Gooberman-Hill R. *Revision Surgery for Prosthetic Hip Joint Infection: Patients' and Surgeons' Views on Treatment and Research.* EFORT; Prague, Czechia, May 2015.

Moore A, Gooberman-Hill R. *Complications after Surgery for Painful Hip Osteoarthritis: A Qualitative Study with Patients and Surgeons.* BPS; Glasgow, UK, April 2015.

Moore A, Gooberman-Hill R. *Deep Prosthetic Joint Infection: Impact on Patient and Preferences for Treatment.* BSR; Manchester, UK, May 2015.

Beswick A. *Infection after Total Hip Replacement. The INFORM Programme.* Zero Tolerance of Surgical Site Infection; Northumberland, UK, October 2016.

Beswick A, Strange S, Lenguerrand E, Moore A, Kunutsor S, Gooberman-Hill R, *et al. One- or Two-stage Revision of Infected Hip Replacements: Is a Randomised Controlled Trial Possible?* COMOC; Cape Town, South Africa, April 2016.

Lenguerrand E. *Increasing Burden of Infection and Risk of Early Revision following Hip and Knee Replacement. Evidence from the National Joint Registry for England and Wales.* EORS; Bologna, Italy, September 2016.

Data-sharing statement

All data requests should be submitted to the corresponding author for consideration. Following review, access to available anonymised data may be granted.

Patient data

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety, and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it is important that there are safeguards to make sure that it is stored and used responsibly. Everyone should be able to find out about how patient data is used. #datasaveslives You can find out more about the background to this citation here: https://understandingpatientdata.org.uk/data-citation.

References

1. Blom AW, Lenguerrand E, Strange S, Noble SM, Beswick AD, Burston A, *et al.* Clinical and cost effectiveness of single stage compared with two stage revision for hip prosthetic joint infection (INFORM): pragmatic, parallel group, open label, randomised controlled trial. *BMJ* 2022;**379**:e071281. https://doi.org/10.1136/bmj-2022-071281

2. Swain S, Sarmanova A, Mallen C, Kuo CF, Coupland C, Doherty M, Zhang W. Trends in incidence and prevalence of osteoarthritis in the United Kingdom: findings from the Clinical Practice Research Datalink (CPRD). *Osteoarthritis Cartilage* 2020;**28**:792–801. https://doi.org/10.1016/j.joca.2020.03.004

3. Barbour KE, Moss S, Croft JB, Helmick CG, Theis KA, Brady TJ, *et al.* Geographic variations in arthritis prevalence, health-related characteristics, and management – United States, 2015. *MMWR Surveill Summ* 2018;**67**:1–28. https://doi.org/10.15585/mmwr.ss6704a1

4. Culliford DJ, Maskell J, Kiran A, Judge A, Javaid MK, Cooper C, Arden NK. The lifetime risk of total hip and knee arthroplasty: results from the UK general practice research database. *Osteoarthritis Cartilage* 2012;**20**:519–24. https://doi.org/10.1016/j.joca.2012.02.636

5. Ackerman IN, Bohensky MA, de Steiger R, Brand CA, Eskelinen A, Fenstad AM, *et al.* Lifetime risk of primary total hip replacement surgery for osteoarthritis from 2003 to 2013: a multinational analysis using national registry data. *Arthritis Care Res* 2017;**69**:1659–67. https://doi.org/10.1002/acr.23197

6. Ackerman IN, Bohensky MA, de Steiger R, Brand CA, Eskelinen A, Fenstad AM, *et al.* Substantial rise in the lifetime risk of primary total knee replacement surgery for osteoarthritis from 2003 to 2013: an international, population-level analysis. *Osteoarthritis Cartilage* 2017;**25**:455–61. https://doi.org/10.1016/j.joca.2016.11.005

7. Burn E, Murray DW, Hawker GA, Pinedo-Villanueva R, Prieto-Alhambra D. Lifetime risk of knee and hip replacement following a GP diagnosis of osteoarthritis: a real-world cohort study. *Osteoarthritis Cartilage* 2019;**27**:1627–35. https://doi.org/10.1016/j.joca.2019.06.004

8. National Joint Registry (NJR). *17th Annual Report*. Hemel Hempstead: NJR Service Centre; 2020. URL: https://reports.njrcentre.org.uk/Portals/0/PDFdownloads/NJR%2017th%20Annual%20Report%202020.pdf (accessed 5 March 2021).

9. Scottish Arthroplasty Project. *Annual Report 2020*. Edinburgh: Public Health Scotland; 2020. URL: https://readymag.com/PHIDigital/SAP-Annual-Report-2020/ (accessed 4 March 2021).

10. Singh JA, Yu S, Chen L, Cleveland JD. Rates of total joint replacement in the United States: future projections to 2020-2040 using the national inpatient sample. *J Rheumatol* 2019;**46**:1134–40. https://doi.org/10.3899/jrheum.170990

11. Blom AW, Brown J, Taylor AH, Pattison G, Whitehouse S, Bannister GC. Infection after total knee arthroplasty. *J Bone Joint Surg Br* 2004;**86**:688–91. https://doi.org/10.1302/0301-620x.86b5.14887

12. Blom AW, Taylor AH, Pattison G, Whitehouse S, Bannister GC. Infection after total hip arthroplasty: the Avon experience. *J Bone Joint Surg Br* 2003;**85**:956–9. https://doi.org/10.1302/0301-620x.85b7.14095

13. Blom AW, Rogers M, Taylor AH, Pattison G, Whitehouse S, Bannister GC. Dislocation following total hip replacement: the Avon Orthopaedic Centre experience. *Ann R Coll Surg Engl* 2008;**90**:658–62. https://doi.org/10.1308/003588408X318156

14. Berry DJ. Epidemiology: hip and knee. *Orthop Clin North Am* 1999;**30**:183–90. https://doi.org/10.1016/S0030-5898(05)70073-0

15. Lapidus LJ, Ponzer S, Pettersson H, de Bri E. Symptomatic venous thromboembolism and mortality in orthopaedic surgery – an observational study of 45 968 consecutive procedures. *BMC Musculoskelet Disord* 2013;**14**:177. https://doi.org/10.1186/1471-2474-14-177

16. Smith TO, Blake V, Hing CB. Minimally invasive versus conventional exposure for total hip arthroplasty: a systematic review and meta-analysis of clinical and radiological outcomes. *Int Orthop* 2011;**35**:173–84. https://doi.org/10.1007/s00264-010-1075-8

17. Hunter G, Dandy D. The natural history of the patient with an infected total hip replacement. *J Bone Joint Surg Br* 1977;**59**:293–7. https://doi.org/10.1302/0301-620X.59B3.893507

18. Zimmerli W, Trampuz A, Ochsner PE. Prosthetic-joint infections. *N Engl J Med* 2004;**351**:1645–54. https://doi.org/10.1056/NEJMra040181

19. Matthews PC, Berendt AR, McNally MA, Byren I. Diagnosis and management of prosthetic joint infection. *BMJ* 2009;**338**:b1773. https://doi.org/10.1136/bmj.b1773

20. Arnold WV, Shirtliff ME, Stoodley P. Bacterial biofilms and periprosthetic infections. *J Bone Joint Surg Am* 2013;**95**:2223–9.

21. Gbejuade HO, Lovering AM, Webb JC. The role of microbial biofilms in prosthetic joint infections. *Acta Orthop* 2015;**86**:147–58. https://doi.org/10.3109/17453674.2014.966290

22. Andersson AE, Bergh I, Karlsson J, Nilsson K. Patients' experiences of acquiring a deep surgical site infection: an interview study. *Am J Infect Control* 2010;**38**:711–17. https://doi.org/10.1016/j.ajic.2010.03.017

23. Cahill JL, Shadbolt B, Scarvell JM, Smith PN. Quality of life after infection in total joint replacement. *J Orthop Surg* 2008;**16**:58–65. https://doi.org/10.1177/230949900801600115

24. Wylde V, Beswick AD, Dennis J, Gooberman-Hill R. Post-operative patient-related risk factors for chronic pain after total knee replacement: a systematic review. *BMJ Open* 2017;**7**:e018105. https://doi.org/10.1136/bmjopen-2017-018105

25. Ong KL, Kurtz SM, Lau E, Bozic KJ, Berry DJ, Parvizi J. Prosthetic joint infection risk after total hip arthroplasty in the Medicare population. *J Arthroplasty* 2009;**24**(Suppl. 6):105–9. https://doi.org/10.1016/j.arth.2009.04.027

26. Choi HJ, Adiyani L, Sung J, Choi JY, Kim HB, Kim YK, *et al.* Five-year decreased incidence of surgical site infections following gastrectomy and prosthetic joint replacement surgery through active surveillance by the Korean Nosocomial Infection Surveillance System. *J Hosp Infect* 2016;**93**:339–46. https://doi.org/10.1016/j.jhin.2015.12.021

27. Huotari K, Peltola M, Jämsen E. The incidence of late prosthetic joint infections: a registry-based study of 112,708 primary hip and knee replacements. *Acta Orthop* 2015;**86**:321–5. https://doi.org/10.3109/17453674.2015.1035173

28. Lindgren V, Gordon M, Wretenberg P, Kärrholm J, Garellick G. Deep infection after total hip replacement: a method for national incidence surveillance. *Infect Control Hosp Epidemiol* 2014;**35**:1491–6. https://doi.org/10.1086/678600

29. Phillips JE, Crane TP, Noy M, Elliott TS, Grimer RJ. The incidence of deep prosthetic infections in a specialist orthopaedic hospital: a 15-year prospective survey. *J Bone Joint Surg Br* 2006;**88**:943–8. https://doi.org/10.1302/0301-620X.88B7.17150

30. Gundtoft PH, Pedersen AB, Schønheyder HC, Møller JK, Overgaard S. One-year incidence of prosthetic joint infection in total hip arthroplasty: a cohort study with linkage of the Danish Hip Arthroplasty Register and Danish Microbiology Databases. *Osteoarthritis Cartilage* 2017;**25**:685–93. https://doi.org/10.1016/j.joca.2016.12.010

31. Dale H, Hallan G, Espehaug B, Havelin LI, Engesaeter LB. Increasing risk of revision due to deep infection after hip arthroplasty. *Acta Orthop* 2009;**80**:639–45. https://doi.org/10.3109/17453670903506658

32. Lenguerrand E, Whitehouse MR, Beswick AD, Jones SA, Porter ML, Blom AW. Revision for prosthetic joint infection following hip arthroplasty: evidence from the National Joint Registry. *Bone Joint Res* 2017;**6**:391–8. https://doi.org/10.1302/2046-3758.66.BJR-2017-0003.R1

33. Jämsen E, Varonen M, Huhtala H, Lehto MU, Lumio J, Konttinen YT, Moilanen T. Incidence of prosthetic joint infections after primary knee arthroplasty. *J Arthroplasty* 2010;**25**:87–92. https://doi.org/10.1016/j.arth.2008.10.013

34. Hijas-Gómez AI, Lucas WC, Checa-García A, Martínez-Martín J, Fahandezh-Saddi H, Gil-de-Miguel Á, *et al.* Surgical site infection incidence and risk factors in knee arthroplasty: a 9-year prospective cohort study at a university teaching hospital in Spain. *Am J Infect Control* 2018;**46**:1335–40. https://doi.org/10.1016/j.ajic.2018.06.010

35. Baier C, Adelmund S, Schwab F, Lassahn C, Chaberny IF, Gossé F, *et al.* Incidence and risk factors of surgical site infection after total knee arthroplasty: results of a retrospective cohort study. *Am J Infect Control* 2019;**47**:1270–2. https://doi.org/10.1016/j.ajic.2019.04.010

36. Lenguerrand E, Whitehouse MR, Beswick AD, Toms AD, Porter ML, Blom AW, National Joint Registry for England, Wales, Northern Ireland and the Isle of Man. Description of the rates, trends and surgical burden associated with revision for prosthetic joint infection following primary and revision knee replacements in England and Wales: an analysis of the National Joint Registry for England, Wales, Northern Ireland and the Isle of Man. *BMJ Open* 2017;**7**:e014056. https://doi.org/10.1136/bmjopen-2016-014056

37. Wang FD, Wang YP, Chen CF, Chen HP. The incidence rate, trend and microbiological aetiology of prosthetic joint infection after total knee arthroplasty: a 13 years' experience from a tertiary medical center in Taiwan. *J Microbiol Immunol Infect* 2018;**51**:717–22. https://doi.org/10.1016/j.jmii.2018.08.011

38. Leone JM, Hanssen AD. Management of infection at the site of a total knee arthroplasty. *Instr Course Lect* 2006;**55**:449–61.

39. Giulieri SG, Graber P, Ochsner PE, Zimmerli W. Management of infection associated with total hip arthroplasty according to a treatment algorithm. *Infection* 2004;**32**:222–8. https://doi.org/10.1007/s15010-004-4020-1

40. Byren I, Bejon P, Atkins BL, Angus B, Masters S, McLardy-Smith P, *et al.* One hundred and twelve infected arthroplasties treated with 'DAIR' (debridement, antibiotics and implant retention): antibiotic duration and outcome. *J Antimicrob Chemother* 2009;**63**:1264–71. https://doi.org/10.1093/jac/dkp107

41. Romanò C, Logoluso N, Drago L, Peccati A, Romanò D. Role for irrigation and debridement in periprosthetic infections. *J Knee Surg* 2014;**27**:267–72. https://doi.org/10.1055/s-0034-1373736

42. Yang FS, Lu YD, Wu CT, Blevins K, Lee MS, Kuo FC. Mechanical failure of articulating polymethylmethacrylate (PMMA) spacers in two-stage revision hip arthroplasty: the risk factors and the impact on interim function. *BMC Musculoskelet Disord* 2019;**20**:372. https://doi.org/10.1186/s12891-019-2759-x

43. Jung J, Schmid NV, Kelm J, Schmitt E, Anagnostakos K. Complications after spacer implantation in the treatment of hip joint infections. *Int J Med Sci* 2009;**6**:265–73. https://doi.org/10.7150/ijms.6.265

44. Gehrke T, Zahar A, Kendoff D. One-stage exchange: it all began here. *Bone Joint J* 2013;**95–B**(Suppl. 11):77–83. https://doi.org/10.1302/0301-620X.95B11.32646

45. Jenny JY, Lengert R, Diesinger Y, Gaudias J, Boeri C, Kempf JF. Routine one-stage exchange for chronic infection after total hip replacement. *Int Orthop* 2014;**38**:2477–81. https://doi.org/10.1007/s00264-014-2466-z

46. Tsung JD, Rohrsheim JA, Whitehouse SL, Wilson MJ, Howell JR. Management of periprosthetic joint infection after total hip arthroplasty using a custom made articulating spacer (CUMARS); the Exeter experience. *J Arthroplasty* 2014;**29**:1813–18. https://doi.org/10.1016/j.arth.2014.04.013

47. Beswick AD, Elvers KT, Smith AJ, Gooberman-Hill R, Lovering A, Blom AW. What is the evidence base to guide surgical treatment of infected hip prostheses? Systematic review of longitudinal studies in unselected patients. *BMC Med* 2012;**10**:18. https://doi.org/10.1186/1741-7015-10-18

48. Blom AW, Artz N, Beswick AD, Burston A, Dieppe P, Elvers KT, *et al.* Improving patients' experience and outcome of total joint replacement: the RESTORE programme. *Programme Grants Appl Res* 2016;**4**(12). https://doi.org/10.3310/pgfar04120

49. INVOLVE. *How to Involve People in Research*. Southampton: INVOLVE; 2015. URL: www.invo.org.uk/find-out-more/how-to-involve-people/ (accessed 19 April 2021).

50. Lenguerrand E, Whitehouse MR, Beswick AD, Kunutsor SK, Burston B, Porter M, Blom AW. Risk factors associated with revision for prosthetic joint infection after hip replacement: a prospective observational cohort study. *Lancet Infect Dis* 2018;**18**:1004–14. https://doi.org/10.1016/S1473-3099(18)30345-1

51. Lenguerrand E, Whitehouse MR, Beswick AD, Kunutsor SK, Foguet P, Porter M, Blom AW, National Joint Registry for England, Wales, Northern Ireland and the Isle of Man. Risk factors associated with revision for prosthetic joint infection following knee replacement: an observational cohort study from England and Wales. *Lancet Infect Dis* 2019;**19**:589–600. https://doi.org/10.1016/S1473-3099(18)30755-2

52. Garfield K, Noble S, Lenguerrand E, Whitehouse MR, Sayers A, Reed MR, Blom AW. What are the inpatient and day case costs following primary total hip replacement of patients treated for prosthetic joint infection: a matched cohort study using linked data from the National Joint Registry and Hospital Episode Statistics. *BMC Med* 2020;**18**:335. https://doi.org/10.1186/s12916-020-01803-7

53. Abouljoud MM, Backstein D, Battenberg A, Dietz M, Erice A, Freiberg AA, *et al.* Hip and knee section, treatment, surgical technique: proceedings of International Consensus on Orthopedic Infections. *J Arthroplasty* 2019;**34**:S445–51. https://doi.org/10.1016/j.arth.2018.09.029

54. Bone and Joint Infection Registry. *BAJIR Bone and Joint Infection Registry*. Wallsend: Northumbria Healthcare NHS Foundation Trust; 2020. URL: https://bajir.org/ (accessed 16 February 2021).

55. Vanhegan IS, Malik AK, Jayakumar P, Ul Islam S, Haddad FS. A financial analysis of revision hip arthroplasty: the economic burden in relation to the national tariff. *J Bone Joint Surg Br* 2012;**94**:619–23. https://doi.org/10.1302/0301-620X.94B5.27073

56. Graves N, Wloch C, Wilson J, Barnett A, Sutton A, Cooper N, *et al.* A cost-effectiveness modelling study of strategies to reduce risk of infection following primary hip replacement based on a systematic review. *Health Technol Assess* 2016;**20**(54). https://doi.org/10.3310/hta20540

57. Moore AJ, Blom AW, Whitehouse MR, Gooberman-Hill R. Deep prosthetic joint infection: a qualitative study of the impact on patients and their experiences of revision surgery. *BMJ Open* 2015;**5**:e009495. https://doi.org/10.1136/bmjopen-2015-009495

58. Mallon CM, Gooberman-Hill R, Moore AJ. Infection after knee replacement: a qualitative study of impact of periprosthetic knee infection. *BMC Musculoskelet Disord* 2018;**19**:352. https://doi.org/10.1186/s12891-018-2264-7

59. Braun V, Clarke V. Using thematic analysis in psychology. *Qual Res Psychol* 2006;**3**:77–101. https://doi.org/10.1191/1478088706qp063oa

60. Moore AJ, Blom AW, Whitehouse MR, Gooberman-Hill R. Managing uncertainty – a qualitative study of surgeons' decision-making for one-stage and two-stage revision surgery for prosthetic hip joint infection. *BMC Musculoskelet Disord* 2017;**18**:154. https://doi.org/10.1186/s12891-017-1499-z

61. Mallon C, Gooberman-Hill R, Blom A, Whitehouse M, Moore A. Surgeons are deeply affected when patients are diagnosed with prosthetic joint infection. *PLOS ONE* 2018;**13**:e0207260. https://doi.org/10.1371/journal.pone.0207260

62. Ruggieri P. *Confessions of a Surgeon: The Good, The Bad and The Complicated. Life Behind the O.R. Doors.* New York, NY: Penguin Group; 2012.

63. Orri M, Farges O, Clavien PA, Barkun J, Revah-Lévy A. Being a surgeon – the myth and the reality: a meta-synthesis of surgeons' perspectives about factors affecting their practice and well-being. *Ann Surg* 2014;**260**:721–8. https://doi.org/10.1097/SLA.0000000000000962

64. Scott SD, Hirschinger LE, Cox KR, McCoig M, Brandt J, Hall LW. The natural history of recovery for the healthcare provider 'second victim' after adverse patient events. *Qual Saf Health Care* 2009;**18**:325–30. https://doi.org/10.1136/qshc.2009.032870

65. Kunutsor SK, Whitehouse MR, Blom AW, Beswick AD, INFORM Team. Patient-related risk factors for periprosthetic joint infection after total joint arthroplasty: a systematic review and meta-analysis. *PLOS ONE* 2016;**11**:e0150866. https://doi.org/10.1371/journal.pone.0150866

66. Kunutsor SK, Beswick AD, Whitehouse MR, Blom AW, Lenguerrand E. Implant fixation and risk of prosthetic joint infection following primary total hip replacement: meta-analysis of observational cohort and randomised intervention studies. *J Clin Med* 2019;**8**:722. https://doi.org/10.3390/jcm8050722

67. Kunutsor SK, Wylde V, Whitehouse MR, Beswick AD, Lenguerrand E, Blom AW. Influence of fixation methods on prosthetic joint infection following primary total knee replacement: meta-analysis of observational cohort and randomised intervention studies. *J Clin Med* 2019;**8**:828. https://doi.org/10.3390/jcm8060828

68. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA Statement. *Open Med* 2009;**3**:e123–30. https://doi.org/10.1371/journal.pmed.1000097

69. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, *et al.* Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA* 2000;**283**:2008–12. https://doi.org/10.1001/jama.283.15.2008

70. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, *et al. The Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Nonrandomised Studies in Meta-analyses.* 2011. URL: www.ohri.ca/programs/clinical_epidemiology/oxford.asp (accessed 19 April 2021).

71. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, *et al.* The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;**343**:d5928. https://doi.org/10.1136/bmj.d5928

72. Goldstein H, Browne W, Rasbash J. Multilevel modelling of medical data. *Stat Med* 2002;**21**:3291–315. https://doi.org/10.1002/sim.1264

73. Blossfeld H, Golsch K, Rohwer G. Models with period-specific effects. In Blossfeld H, Golsch K, Rohwer G, editors. *Event History Analysis with Stata*. Hove: Psychology Press; 2009. pp. 123–7.

74. Sera F, Ferrari P. A multilevel model to estimate the within- and the between-center components of the exposure/disease association in the EPIC study. *PLOS ONE* 2015;**10**:e0117815. https://doi.org/10.1371/journal.pone.0117815

75. Hannske M, Tscherne H. [Results of prophylactic use of Refobacin-Palacos in implantation of endoprostheses of the hip joint in Hannover.] *Aktuelle Probl Chir Orthop* 1979;**12**:201–5.

76. Hinarejos P, Guirro P, Leal J, Montserrat F, Pelfort X, Sorli ML, *et al.* The use of erythromycin and colistin-loaded cement in total knee arthroplasty does not reduce the incidence of infection: a prospective randomized study in 3000 knees. *J Bone Joint Surg Am* 2013;**95**:769–74. https://doi.org/10.2106/JBJS.L.00901

77. Hsieh PH, Lee MS, Hsu KY, Chang YH, Shih HN, Ueng SW. Gram-negative prosthetic joint infections: risk factors and outcome of treatment. *Clin Infect Dis* 2009;**49**:1036–43. https://doi.org/10.1086/605593

78. Wyatt MC, Beswick AD, Kunutsor SK, Wilson MJ, Whitehouse MR, Blom AW. The alpha-defensin immunoassay and leucocyte esterase colormetric strip test as diagnostic tests in periprosthetic infection: a systematic review and meta-analysis. *J Bone Joint Surg Am* 2016;**98**:992–1000. https://doi.org/10.2106/JBJS.15.01142

79. Buntinx F, Aertgeerts B, Macaskill P. Guidelines for conducting systematic reviews of studies evaluating the accuracy of diagnostic tests. In Knottnerus JA, Buntinx F, editors. *The Evidence Base of Clinical Diagnosis: Theory and Methods of Diagnostic Research*. 2nd edn. London: Wiley-Blackwell; 2009. pp. 180–212. https://doi.org/10.1002/9781444300574.ch10

80. Reitsma JB, Glas AS, Rutjes AW, Scholten RJ, Bossuyt PM, Zwinderman AH. Bivariate analysis of sensitivity and specificity produces informative summary measures in diagnostic reviews. *J Clin Epidemiol* 2005;**58**:982–90. https://doi.org/10.1016/j.jclinepi.2005.02.022

81. Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, *et al.* QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Ann Intern Med* 2011;**155**:529–36. https://doi.org/10.7326/0003-4819-155-8-201110180-00009

82. Carli AV, Abdelbary H, Ahmadzai N, Cheng W, Shea B, Hutton B, *et al.* Diagnostic accuracy of serum, synovial, and tissue testing for chronic periprosthetic joint infection after hip and knee replacements: a systematic review. *J Bone Joint Surg Am* 2019;**101**:635–49. https://doi.org/10.2106/JBJS.18.00632

83. Health Technology Wales. *Synovasure® Alpha Defensin Test for Diagnosing Periprosthetic Joint Infection*. Cardiff: Health Technology Wales; 2019. URL: www.healthtechnology.wales/wp-content/uploads/2019/03/EAR008-Synovasure.pdf (accessed 19 April 2021).

84. Parvizi J, Tan TL, Goswami K, Higuera C, Della Valle C, Chen AF, Shohat N. The 2018 definition of periprosthetic hip and knee infection: an evidence-based and validated criteria. *J Arthroplasty* 2018;**33**:1309–14.e2. https://doi.org/10.1016/j.arth.2018.02.078

85. Kunutsor SK, Beswick AD, Whitehouse MR, Wylde V, Blom AW. Debridement, antibiotics and implant retention for periprosthetic joint infections: a systematic review and meta-analysis of treatment outcomes. *J Infect* 2018;**77**:479–88. https://doi.org/10.1016/j.jinf.2018.08.017

86. Kunutsor SK, Whitehouse MR, Blom AW, Beswick AD, INFORM Team. Re-infection outcomes following one- and two-stage surgical revision of infected hip prosthesis: a systematic review and meta-analysis. *PLOS ONE* 2015;**10**:e0139166. https://doi.org/10.1371/journal.pone.0139166

87. Kunutsor SK, Whitehouse MR, Lenguerrand E, Blom AW, Beswick AD, INFORM Team. Re-Infection outcomes following one- and two-stage surgical revision of infected knee prosthesis: a systematic review and meta-analysis. *PLOS ONE* 2016;**11**:e0151537. https://doi.org/10.1371/journal.pone.0151537

88. Kunutsor SK, Whitehouse MR, Blom AW, Board T, Kay P, Wroblewski BM, *et al.* One- and two-stage surgical revision of peri-prosthetic joint infection of the hip: a pooled individual participant data analysis of 44 cohort studies. *Eur J Epidemiol* 2018;**33**:933–46. https://doi.org/10.1007/s10654-018-0377-9

89. Slim K, Nini E, Forestier D, Kwiatkowski F, Panis Y, Chipponi J. Methodological index for non-randomized studies (MINORS): development and validation of a new instrument. *ANZ J Surg* 2003;**73**:712–16. https://doi.org/10.1046/j.1445-2197.2003.02748.x

90. Freeman MF, Tukey JW. Transformations related to the angular and the square root. *Ann Math Statist* 1950;**21**:607–11. https://doi.org/10.1214/aoms/1177729756

91. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;**315**:629–34. https://doi.org/10.1136/bmj.315.7109.629

92. Cochrane Collaboration Individual Patient Data Meta-analysis Methods Group. *FAQs (Frequently Asked Questions) on IPD Meta-analysis*. 2007. URL: https://methods.cochrane.org/ipdma/frequently-asked-questions (accessed 4 March 2021).

93. Riley RD, Lambert PC, Abo-Zaid G. Meta-analysis of individual participant data: rationale, conduct, and reporting. *BMJ* 2010;**340**:c221. https://doi.org/10.1136/bmj.c221

94. Stewart LA, Clarke M, Rovers M, Riley RD, Simmonds M, Stewart G, Tierney JF, PRISMA-IPD Development Group. Preferred Reporting Items for Systematic Review and Meta-Analyses of individual participant data: the PRISMA-IPD Statement. *JAMA* 2015;**313**:1657–65. https://doi.org/10.1001/jama.2015.3656

95. Kunutsor SK, Whitehouse MR, Webb J, Toms A, Stockley I, Taylor A, *et al.* Re-infection outcomes following one- and two-stage surgical revision of infected hip prosthesis in unselected patients: protocol for a systematic review and an individual participant data meta-analysis. *Syst Rev* 2015;**4**:58. https://doi.org/10.1186/s13643-015-0044-0

96. Hougaard P. Frailty models for survival data. *Lifetime Data Anal* 1995;**1**:255–73. https://doi.org/10.1007/BF00985760

97. Strange S, Whitehouse MR, Beswick AD, Board T, Burston A, Burston B, *et al.* One-stage or two-stage revision surgery for prosthetic hip joint infection – the INFORM trial: a study protocol for a randomised controlled trial. *Trials* 2016;**17**:90. https://doi.org/10.1186/s13063-016-1213-8

98. Wylde V, Lenguerrand E, Gooberman-Hill R, Beswick AD, Marques E, Noble S, *et al.* Effect of local anaesthetic infiltration on chronic postsurgical pain after total hip and knee replacement: the APEX randomised controlled trials. *Pain* 2015;**156**:1161–70. https://doi.org/10.1097/j.pain.0000000000000114

99. White IR, Royston P, Wood AM. Multiple imputation using chained equations: issues and guidance for practice. *Stat Med* 2011;**30**:377–99. https://doi.org/10.1002/sim.4067

100. Bellamy N, Hochberg M, Tubach F, Martin-Mola E, Awada H, Bombardier C, *et al.* Development of multinational definitions of minimal clinically important improvement and patient acceptable symptomatic state in osteoarthritis. *Arthritis Care Res* 2015;**67**:972–80. https://doi.org/10.1002/acr.22538

101. NHS Improvement. *NHS Reference Costs 2018 to 2019*. London: NHS England; 2020. URL: www.england.nhs.uk/publication/2018-19-national-cost-collection-data-publication (accessed 19 November 2020).

102. Curtis L, Burns A. *Unit Costs of Health and Social Care 2019*. Canterbury: Personal Social Services Research Unit, University of Kent; 2019. URL: www.pssru.ac.uk/project-pages/unit-costs/unit-costs-2019 (accessed 19 November 2020).

103. Office for National Statistics. *Annual Survey of Hours and Earnings (ASHE)*. Newport: Office for National Statistics; 2019. URL: www.ons.gov.uk/surveys/informationforbusinesses/businesssurveys/annualsurveyofhoursandearningsashe (accessed 2 March 2021).

104. EuroQol Research Foundation. *EQ-5D-5L Valuation Crosswalk Index Value Calculator*. Rotterdam: EuroQol Research Foundation; 2020. URL: https://euroqol.org/eq-5d-instruments/eq-5d-5l-about/valuation-standard-value-sets/crosswalk-index-value-calculator/ (accessed 5 March 2021).

105. Manca A, Hawkins N, Sculpher MJ. Estimating mean QALYs in trial-based cost-effectiveness analysis: the importance of controlling for baseline utility. *Health Econ* 2005;**14**:487–96. https://doi.org/10.1002/hec.944

106. White IR, Thompson SG. Adjusting for partially missing baseline measurements in randomized trials. *Stat Med* 2005;**24**:993–1007. https://doi.org/10.1002/sim.1981

107. Greene WH. *Econometric Analysis*. 5th edn. Hoboken, NJ: Prentice Hall; 2002.

108. Palmer CK, Gooberman-Hill R, Blom AW, Whitehouse MR, Moore AJ. Post-surgery and recovery experiences following one- and two-stage revision for prosthetic joint infection – a qualitative study of patients' experiences. *PLOS ONE* 2020;**15**:e0237047. https://doi.org/10.1371/journal.pone.0237047

109. Carroll FE, Gooberman-Hill R, Strange S, Blom AW, Moore AJ. What are patients' preferences for revision surgery after periprosthetic joint infection? A discrete choice experiment. *BMJ Open* 2020;**10**:e031645. https://doi.org/10.1136/bmjopen-2019-031645

110. Lancsar E, Louviere J. Conducting discrete choice experiments to inform healthcare decision making: a user's guide. *PharmacoEconomics* 2008;**26**:661–77. https://doi.org/10.2165/00019053-200826080-00004

111. Coast J, Al-Janabi H, Sutton EJ, Horrocks SA, Vosper AJ, Swancutt DR, Flynn TN. Using qualitative methods for attribute development for discrete choice experiments: issues and recommendations. *Health Econ* 2012;**21**:730–41. https://doi.org/10.1002/hec.1739

112. Kuhfeld WF. Construction of efficient designs for discrete choice experiments. In Grover R, Vriens M, editors. *The Handbook of Marketing Research*. Thousand Oaks, CA: SAGE Publications, Inc.; 2006. pp. 312–29. https://doi.org/10.4135/9781412973380.n16

113. Bech M, Gyrd-Hansen D. Effects coding in discrete choice experiments. *Health Econ* 2005;**14**:1079–83. https://doi.org/10.1002/hec.984

114. Evers S, Goossens M, de Vet H, van Tulder M, Ament A. Criteria list for assessment of methodological quality of economic evaluations: Consensus on Health Economic Criteria. *Int J Technol Assess Health Care* 2005;**21**:240–5. https://doi.org/10.1017/S0266462305050324

115. Alp E, Cevahir F, Ersoy S, Guney A. Incidence and economic burden of prosthetic joint infections in a university hospital: a report from a middle-income country. *J Infect Public Health* 2016;**9**:494–8. https://doi.org/10.1016/j.jiph.2015.12.014

116. Assmann G, Kasch R, Maher CG, Hofer A, Barz T, Merk H, Flessa S. Comparison of health care costs between aseptic and two stage septic hip revision. *J Arthroplasty* 2014;**29**:1925–31. https://doi.org/10.1016/j.arth.2014.04.043

117. Bozic KJ, Ries MD. The impact of infection after total hip arthroplasty on hospital and surgeon resource utilization. *J Bone Joint Surg Am* 2005;**87**:1746–51. https://doi.org/10.2106/00004623-200508000-00012

118. Gow N, McGuinness C, Morris AJ, McLellan A, Morris JT, Roberts SA. Excess cost associated with primary hip and knee joint arthroplasty surgical site infections: a driver to support investment in quality improvement strategies to reduce infection rates. *N Z Med J* 2016;**129**:51–8.

119. Haenle M, Skripitz C, Mittelmeier W, Skripitz R. [Economic impact of infected total hip arthroplasty in the German diagnosis-related groups system.] *Orthopade* 2012;**41**:467–76. https://doi.org/10.1007/s00132-012-1939-2

120. Haenle M, Skripitz C, Mittelmeier W, Skripitz R. Economic impact of infected total knee arthroplasty. *ScientificWorldJournal* 2012;**2012**:196515. https://doi.org/10.1100/2012/196515

121. Kallala RF, Vanhegan IS, Ibrahim MS, Sarmah S, Haddad FS. Financial analysis of revision knee surgery based on NHS tariffs and hospital costs: does it pay to provide a revision service? *Bone Joint J* 2015;**97–B**:197–201. https://doi.org/10.1302/0301-620X.97B2.33707

122. Kapadia BH, McElroy MJ, Issa K, Johnson AJ, Bozic KJ, Mont MA. The economic impact of periprosthetic infections following total knee arthroplasty at a specialized tertiary-care center. *J Arthroplasty* 2014;**29**:929–32. https://doi.org/10.1016/j.arth.2013.09.017

123. Kapadia BH, Banerjee S, Cherian JJ, Bozic KJ, Mont MA. The economic impact of periprosthetic infections after total hip arthroplasty at a specialized tertiary-care center. *J Arthroplasty* 2016;**31**:1422–6. https://doi.org/10.1016/j.arth.2016.01.021

124. Klouche S, Sariali E, Mamoudy P. Total hip arthroplasty revision due to infection: a cost analysis approach. *Orthop Traumatol Surg Res* 2010;**96**:124–32. https://doi.org/10.1016/j.rcot.2010.02.005

125. Merollini KM, Crawford RW, Graves N. Surgical treatment approaches and reimbursement costs of surgical site infections post hip arthroplasty in Australia: a retrospective analysis. *BMC Health Serv Res* 2013;**13**:91. https://doi.org/10.1186/1472-6963-13-91

126. Oduwole KO, Molony DC, Walls RJ, Bashir SP, Mulhall KJ. Increasing financial burden of revision total knee arthroplasty. *Knee Surg Sports Traumatol Arthrosc* 2010;**18**:945–8. https://doi.org/10.1007/s00167-010-1074-8

127. Peel TN, Cheng AC, Lorenzo YP, Kong DC, Buising KL, Choong PF. Factors influencing the cost of prosthetic joint infection treatment. *J Hosp Infect* 2013;**85**:213–19. https://doi.org/10.1016/j.jhin.2013.07.012

128. Rennert-May ED, Conly J, Smith S, Puloski S, Henderson E, Au F, Manns B. The cost of managing complex surgical site infections following primary hip and knee arthroplasty: a population-based cohort study in Alberta, Canada. *Infect Control Hosp Epidemiol* 2018;**39**:1183–8. https://doi.org/10.1017/ice.2018.199

129. Romano CL, Romano D, Logoluso N, Meani E. Septic versus aseptic hip revision: how different? *J Orthop Traumatol* 2010;**11**:167–74. https://doi.org/10.1007/s10195-010-0106-y

130. Peel TN, Dowsey MM, Buising KL, Liew D, Choong PF. Cost analysis of debridement and retention for management of prosthetic joint infection. *Clin Microbiol Infect* 2013;**19**:181–6. https://doi.org/10.1111/j.1469-0691.2011.03758.x

131. Kalore NV, Maheshwari A, Sharma A, Cheng E, Gioe TJ. Is there a preferred articulating spacer technique for infected knee arthroplasty? A preliminary study. *Clin Orthop Relat Res* 2012;**470**:228–35. https://doi.org/10.1007/s11999-011-2037-1

132. Nodzo SR, Boyle KK, Spiro S, Nocon AA, Miller AO, Westrich GH. Success rates, characteristics, and costs of articulating antibiotic spacers for total knee periprosthetic joint infection. *Knee* 2017;**24**:1175–81. https://doi.org/10.1016/j.knee.2017.05.016

133. Jämsen E, Stogiannidis I, Malmivaara A, Pajamäki J, Puolakka T, Konttinen YT. Outcome of prosthesis exchange for infected knee arthroplasty: the effect of treatment approach. *Acta Orthop* 2009;**80**:67–77. https://doi.org/10.1080/17453670902805064

134. Melo L. *REVISITS: Revision Single or Two Stage Surgery (REVISITS)*. ClinicalTrials.gov; 2018. URL: https://clinicaltrials.gov/ct2/show/NCT03741296 (accessed 3 August 2022).

135. Odum S, Cadd C. *One Stage versus Two Stage for Periprosthetic Hip and Knee Infection*. ClinicalTrials.gov; 2016. URL: https://clinicaltrials.gov/ct2/show/NCT02734134 (accessed 3 August 2022).

136. Scharfenberger A, Clark M, Lavoie G, O'Connor G, Masson E, Beaupre LA. Treatment of an infected total hip replacement with the PROSTALAC system. Part 2: health-related quality of life and function with the PROSTALAC implant in situ. *Can J Surg* 2007;**50**:29–33.

137. Curtis L. *Unit Costs of Health and Social Care 2013*. Canterbury: Personal Social Services Research Unit, University of Kent; 2013. URL: www.pssru.ac.uk/project-pages/unit-costs/unit-costs-2013/ (accessed 3 August 2022).

138. Curtis L, Burns A. *Unit Costs of Health and Social Care 2018*. Canterbury: Personal Social Services Research Unit, University of Kent; 2018. URL: www.pssru.ac.uk/project-pages/unit-costs/unit-costs-2018/ (accessed 3 August 2022).

139. Curtis L, Burns A. *Unit Costs of Health and Social Care 2015*. Canterbury: Personal Social Services Research Unit, University of Kent; 2015. URL: www.pssru.ac.uk/project-pages/unit-costs/unit-costs-2015/ (accessed 3 August 2022).

140. Turner J, O'Cathain A, Knowles E, Nicholl J, Tosh J, Sampson F, *et al. Evaluation of NHS 111 Pilot Sites. Final Report*. University of Sheffield: Medical Care Research Unit; 2012. URL: http://data.parliament.uk/DepositedPapers/Files/DEP2012-1694/HL3309-LibDoc.pdf (accessed 9 September 2022).

141. National Institute for Health and Care Excellence (NICE). *British National Formulary*. London: NICE; 2020. URL: https://bnf.nice.org.uk/ (accessed 3 August 2022).

142. NHS. *Am I Entitled to Free Prescriptions?* London: NHS; 2020. URL: www.nhs.uk/using-the-nhs/help-with-health-costs/get-help-with-prescription-costs/ (accessed 3 August 2022).

143. *NRS Healthcare*. Coalville: NRS Healthcare; 2020. URL: www.healthcarepro.co.uk (accessed 9 September 2022).

144. Office for National Statistics. *Annual Survey of Hours and Earnings (ASHE)*. Newport: Office for National Statistics; 2020. URL: www.ons.gov.uk/surveys/informationforbusinesses/businesssurveys/annualsurveyofhoursandearningsashe (accessed 3 August 2022).

145. NHS Employers. *NHS Terms and Conditions of Service Handbook*. London: The NHS Staff Council; 2019. URL: www.nhsemployers.org/employershandbook/tchandbook/afc_tc_of_service_handbook_fb.pdf (accessed 16 August 2022).

146. National Institute for Health and Care Excellence (NICE). *Guide to the Methods of Technology Appraisal 2013*. Process and Methods [PMG9]. London: NICE; 2013.

147. Briggs AH. A Bayesian approach to stochastic cost-effectiveness analysis. *Health Econ* 1999;**8**:257–61. https://doi.org/10.1002/(SICI)1099-1050(199905)8:3<257::AID-HEC427>3.0.CO;2-E

148. Huber J, Zwerina K. The importance of utility balance in efficient choice designs. *J Mark Res* 1996;**33**:307–17. https://doi.org/10.1177/002224379603300305

Appendix 1 Incidence of prosthetic joint infection after hip or knee replacement

Authors, year; country; dates of data collection	Population	Outcome and rate of infection (follow-up period)	Methodological quality concerns and notes
Hip replacement *Infection outcome*			
Ong *et al.*,[25] 2009; USA; 1997–2006 Multicentre cohort study (prospective registration)	*n* = 28,544 Elective THR Medicare 5% national sample administrative claims database Aged ≥ 65 years	PJI (ICD-10 996.66) identified in claims records from inpatient, outpatient, carrier, skilled nursing facility, hospice care, home health, and durable medical equipment analytic data files 0.78% (2 years) 1.11% (10 years)	None Including non-elective (bone cancer, joint infection, fracture) and elective THR (*n* = 39,929) the 2-year infection rate was 1.63%, 10-year rate 2.22%
Choi *et al.*,[26] 2016; Republic of Korea; 2008–12 National infection surveillance system	*n* = 7656 THR including trauma and reoperation	Infection monitoring during hospital admission and after discharge by surgeons, surgical nurses, infectious diseases physicians and infection control practitioners 2.09% (1 year)	None 2.9% in 2008; 3.1% in 2009; 1.7% in 2010; 2.2% in 2011; 1.5% in 2012
Huotari *et al.*,[27] 2015; Finland; 1998–2009 Joint registries	*n* = 50,272 THR for osteoarthritis	Revision and resection operations identified in joint registries and diagnosis of PJI or wound infection from hospital discharge register 0.71% (2 years) 0.92% (median 5 years; range 1–13 years)	None
Lindgren *et al.*,[28] 2014; Sweden; 2005–8 Joint registry	*n* = 45,531 (49,219 THRs)	Patients with 4 weeks' continuous outpatient antibiotic treatment within 2 years of THR in the Swedish Prescribed Drug Register 0.9% (95% CI 0.85% to 1.02%) (2 years)	None
Phillips *et al.*,[29] 2006; UK; 1987–2001 Single-centre (20 consultants) prospective cohort	*n* = 5947 Primary THR	Positive cultures in microbiology laboratory 0.57% (up to 15 years)	Single centre
Blom *et al.*,[12] 2003; UK; 1993–6 Single-centre retrospective cohort	*n* = 1727 (91% followed up) Primary THR	Postal questionnaire on infection. Hospital notes of patients who died 1.08% (reviewed 5–8 years after surgery)	Single centre, retrospective

Authors, year; country; dates of data collection	Population	Outcome and rate of infection (follow-up period)	Methodological quality concerns and notes
Revision for infection outcome			
Dale et al.,[31] 2009; Norway; 1987–2007 Joint registry	n = 97,344 Primary THR	Revisions for deep infection recorded in joint registry 0.54% (5 years)	None Risk of revision increased from 0.3% to 0.9% between 1987–92 and 2003–7 (adjusted risk ratio 3.0, 95% CI 2.2 to 4.0)
Lenguerrand et al.,[32] 2017; UK; 2003–14 Joint registry	n = 623,253 Primary THR	Revision surgery for PJI recorded in joint registry 0.15% (1 year) 0.26% (2 years) 0.44% (5 years) 0.62% (10 years)	None
Gundtoft et al.,[30] 2017; Denmark; 2005–14 Region from joint registry	n = 48,867 Primary THR	Revision operation with ≥ 3 positive intraoperative cultures 0.55% (1 year)	None 0.53% (95% CI 0.44 to 0.63) during 2005–9; 0.57% (95% CI 0.49 to 0.67) during 2010–14
Blom et al.,[12] 2003; UK; 1993–6 Single-centre retrospective cohort	n = 1727 (91% followed up) Primary THR	Postal questionnaire on infection. Hospital notes of patients who died 0.45% (reviewed 5–8 years after surgery)	Single centre, retrospective
Knee replacement *Infection outcome*			
Huotari et al.,[27] 2015; Finland; 1998–2009 Joint registries	n = 62,436 TKR for osteoarthritis	Revision and resection operations identified in joint registries and diagnosis of PJI or wound infection from hospital discharge register 1.14% (2 years) 1.41% (median 5 years; range 1–13 years)	None
Choi et al.,[26] 2016; Republic of Korea; 2008–12 National infection surveillance system	n = 7648 TKR including trauma and reoperation	Infection monitoring during hospital admission and after discharge by surgeons, surgical nurses, infectious diseases physicians and infection control practitioners 1.9% (1 year)	None 2.9% in 2008; 2.9% in 2009; 1.5% in 2010; 1.9% in 2011; 1.2% in 2012
Jämsen et al.,[33] 2010; Finland; 2002–6 Single-centre prospective cohort	n = 2647 Elective primary TKR	Infections recorded in hospital infection register 0.80% (1 year)	Single centre

Authors, year; country; dates of data collection	Population	Outcome and rate of infection (follow-up period)	Methodological quality concerns and notes
Phillips et al.,[29] 2006; UK; 1987–2001 Single-centre prospective cohort	n = 4788 Primary TKR	Positive cultures in microbiology laboratory 0.86% (up to 15 years)	Single centre
Hijas-Gómez et al.,[34] 2018; Spain; 2008–16 Single-centre prospective cohort	n = 1969 Primary and revision TKR	Surgical site infection surveillance (CDC criteria) 1.0% (90 days)	Single centre, also includes revision TKR; 5% of infections superficial
Blom et al.,[11] 2004; UK; 1993–6 Single-centre retrospective cohort	n = 931 (97% of 956 followed up) Primary TKR	Postal questionnaire on infection. Hospital notes of patients who died 0.97% (mean 6.5 years)	Single centre, retrospective
Baier et al.,[35] 2019; Germany; 2007–10 Single-centre retrospective cohort	n = 2439 Elective TKR. Patients with existing knee infection who died within 3 days or had incomplete data excluded	Periprosthetic joint infection (not including superficial incisional infections). Identified during hospital stay, outpatient visits and readmissions 3.08% (1 year)	Single centre, retrospective Rate decreased from 4.4% in 2007 to 2.5% in 2010 (including superficial incisional infections)
Revision for infection outcome			
Lenguerrand et al.,[36] 2017; UK; 2003–14 Joint registry	n = 679,010 Primary TKR	Revision surgery for PJI recorded in joint registry 0.32% (2 years)	None
Wang et al.,[37] 2018; Taiwan (Province of China); 2002–14 Single-centre retrospective cohort	n = 10,768 Primary TKR. Aged ≥ 18 years	Infection requiring surgical intervention 0.41% (3 months); 0.54% (6 months); 0.79% (1 year); 1.19% (2 years); 1.54% (5 years)	Single centre; 5-year follow-up included patients with TKR (2002–12)

CDC, Centers for Disease Control and Prevention; ICD-10, *International Statistical Classification of Diseases and Related Health Problems,* Tenth Revision; PJI, prosthetic joint infection; THR, total hip replacement; TKR, total knee replacement.

Appendix 2 Health economic consequences of prosthetic joint infection treatment: systematic review

In this appendix we provide further details of the systematic review described in *The significance of prosthetic joint infection to health care*.

Background

Different surgical methods to treat prosthetic joint infection have economic implications for health-care providers and patients. Health services and decision-makers need robust information identifying interventions that provide greatest value for money. Our aim was to identify and critically evaluate the available economic evidence to guide the surgical revision of prosthetic joint infection after hip and knee replacement.

Methods

The systematic review protocol was registered as PROSPERO CRD42017069526.

Eligibility criteria
Eligible studies satisfied the PICOS (population, intervention, comparison, outcomes and study) criteria:

- patients with hip or knee prosthetic joint infection after primary replacement or aseptic revision
- intervention relating to revision surgery
- comparator with no prosthetic joint infection or alternative surgical treatment
- outcome of cost-effectiveness or comparative costs
- full economic evaluation or cost comparison study.

Database searches
We searched MEDLINE and EMBASE on Ovid to 10 April 2019 using the search strategy shown in *Box 2*. Studies included in our other systematic reviews were inspected. No language restrictions were applied, and translations were made as required. Studies reported only as abstracts or unobtainable by interlibrary loans and author contact were excluded.

Screening and data extraction
We imported records into EndNote X9 (Clarivate Analytics, Philadelphia, PA, USA). After an initial screen by one reviewer to exclude clearly irrelevant articles, abstracts were screened independently by at least two reviewers and reasons for exclusion were recorded.

Data were extracted into a Microsoft Excel spreadsheet by two reviewers, specifically country, dates, setting, participants, surgical intervention, currency, date of costs, source of cost data and costs included or excluded in the overall cost estimate. We included only studies that had attempted to calculate costings in their cohort.

Data analysis
The results were tabulated and comparative costs were calculated.

BOX 2 Economic evaluations of revision surgery for prosthetic hip or knee infection: search strategy as applied in MEDLINE via Ovid

---

1. Arthroplasty, Replacement, Knee/or Arthroplasty, Replacement, Hip/
2. exp Arthroplasty, Replacement, Hip/or exp Hip Prosthesis/or hip replacement.mp.
3. exp Arthroplasty, Replacement, Knee/or exp Knee Prosthesis/or knee replacement.mp.
4. knee prosthesis.mp. or exp Knee Prosthesis/
5. hip prosthesis.mp. or exp Hip Prosthesis/
6. total hip.tw.
7. total knee.tw.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. INFECTION/or SURGICAL WOUND INFECTION/or infection.mp. or WOUND INFECTION/
10. infect$.tw.
11. 9 or 10
12. 8 and 11

Cost terms (modified from https://hiru.mcmaster.ca/hiru/HIRU_Hedges_MEDLINE_Strategies.aspx#Economics)

13. cost$.mp. or "Costs and Cost Analysis"/
14. cost benefit analys$.tw.
15. health care costs.mp. or Health Care Costs/
16. ECONOMICS/or economic.mp. or ECONOMICS, MEDICAL/
17. economic.tw.
18. 13 or 14 or 15 or 16 or 17
19. 12 and 18

Quality assessment

To assess risk of bias in cohorts, we used a checklist to assess selection bias.[24] We considered inclusion of consecutive patients and representativeness, and completeness of both follow-up and cost information. To assess studies that had compared costs of revision strategies, we used the Consensus on Health Economic Criteria checklist (CHEC-list).[114]

Results

Review progress is summarised in *Figure 17*. After detailed evaluation, 19 studies were included in the review. Fifteen studies reported cost comparisons of revision procedures for prosthetic joint infection with primary joint replacement or aseptic revision. One of these and two further studies presented different costs associated with single-stage and two-stage revision procedures. In two studies, costs associated with different spacers were compared. Quality assessment is summarised in *Table 9*.

Cost comparisons of prosthetic joint infection revision procedures with primary joint replacement or aseptic revision

Details of the 15 studies reporting cost comparisons of surgical treatments for infection after hip or knee replacement are summarised in *Table 10*.[55,115–124,126,128–130] Studies were conducted in Germany ($n = 3$),[116,119,120] the USA ($n = 3$),[117,122,123] and the UK ($n = 2$),[55,121] with one each in Australia,[130] Canada,[128] France,[124] Ireland,[126] Italy,[129] New Zealand[118] and Turkey.[115] Thirteen studies were conducted in a single hospital site,[55,115–124,126,130] one was conducted in two hospitals[129] and one was conducted in hospitals contributing to a regional database.[128] Seven studies focused on hip infection,[55,116,117,119,123,124,129] four focused on knee infection[120–122,126] and four focused on both hip and knee infection.[115,118,128,130] In six studies the costs of any surgical treatment were reported,[55,118–120,124,128] in seven studies treatment was by a two-stage revision,[116,117,121–123,126,129] and in two studies treatment was with DAIR[130] or predominantly with DAIR.[115]
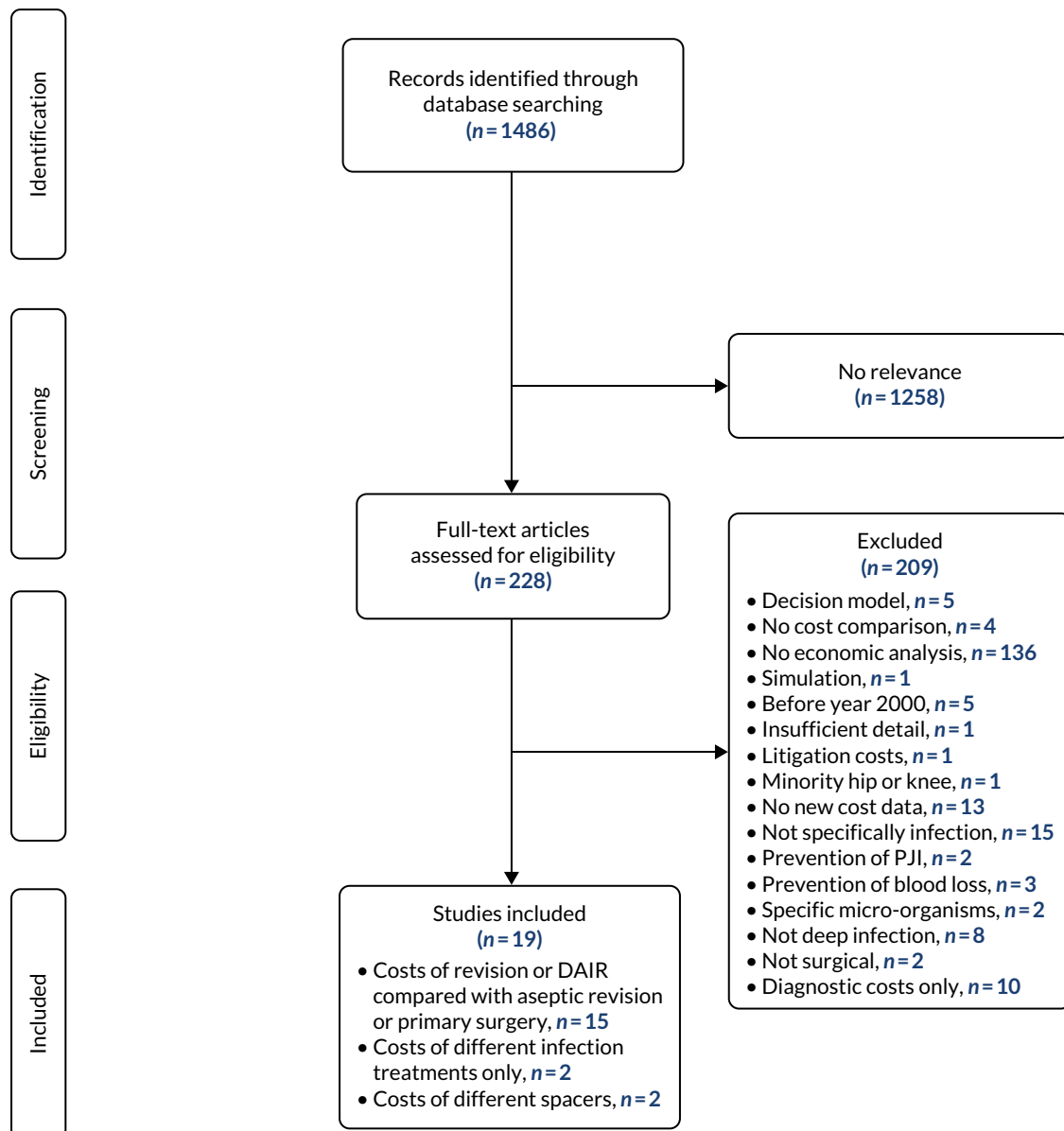
FIGURE 17 Economic evaluations of revision surgery for prosthetic hip or knee infection: systematic review flow diagram. PJI, prosthetic joint infection.

The resources included in cost calculations varied considerably, but no study reported the costs to patients. Generally, the focus was on in-hospital costs.

Risk of bias arose as many studies reported cost information limited to specific aspects of hospital care. As we only report cost comparisons between treatments within centres, this is not a major concern. Studies were mainly in single centres and reported consecutive patients.

Cost of infection treatment compared with cost of primary hip or knee replacement

Eight studies[117–120,122–124,128] reported comparisons between primary hip or knee replacement and first surgical treatments of infected hip or knee replacements other than DAIR. None of the studies was conducted in the UK. The cost of treatments for infection was on average 4.0 times (range 2.9–5.3 times) that of primary hip or knee replacement. The cost of DAIR treatment was on average 3.0 times (range 2.9–3.1 times) that of primary hip or knee replacement.

TABLE 9 Quality assessment of cohort studies

Authors, year	Inclusion of consecutive patients	Representativeness	Completeness of follow-up	Completeness of cost information	Concerns
Alp et al.,[115] 2016	Unclear	Single hospital	Unclear	Partial	No costs for surgeon, anaesthesiologist, infection specialist, physiotherapists, nurses, caregivers, physical therapy
Assmann et al.,[116] 2014	Consecutive	Single hospital	None specified	Partial	No fixed hospital costs
Bozic and Ries,[117] 2005	Consecutive	Single hospital (two surgeons)	None specified	Reasonable	
Gow et al.,[118] 2016	Consecutive	Single hospital	None specified	Reasonable	
Haenle et al.,[119] 2012	Consecutive	Single hospital	None specified	Reasonable	
Haenle et al.,[120] 2012	Consecutive	Single hospital	None specified	Reasonable	
Kallala et al.,[121] 2015	No (complete data only)	Single hospital	None specified	Reasonable	
Kapadia et al.,[122] 2014	Consecutive	Single hospital	None specified	Reasonable	
Kapadia et al.,[123] 2016	Consecutive	Single hospital	None specified	Reasonable	
Klouche et al.,[124] 2010	Consecutive	Single hospital	None specified	Reasonable	
Merollini et al.,[125] 2013	Consecutive	Regional database	None specified	Partial	No costs for antibiotics, primary care, travel, pharmaceuticals, indirect costs
Oduwole et al.,[126] 2010	95% of patients	Single hospital	None specified	Reasonable	
Peel et al.,[127] 2013	Excluding patients who died and < 3 months follow-up	10 hospitals	None specified	Reasonable	
Rennert-May et al.,[128] 2018	Consecutive	Regional database	None specified	Reasonable	
Romano et al.,[129] 2010	Unclear	Two hospitals	3 out of 80	Reasonable	
Vanhegan et al.,[55] 2012	Consecutive	Single hospital	None specified	Reasonable	

In one study that included the costs of primary hip or knee replacement and subsequent first treatments for infection, including those occurring during primary admission, costs were 2.9 times those of primary hip or knee replacement.[118]

Only the cost of the first treatment for hip infection was measured in one study,[124] and this was 3.6 times the cost of primary hip replacement.

TABLE 10 Economic evaluations of revision surgery for prosthetic hip or knee infection: cost-comparison studies

Authors and year; country; recruitment dates; setting; risk-of-bias concerns	Indication; number of patients; follow-up; comparator group	Year (cost); currency; source of data	Costs included	Costs that studies state are not included	Costs with description of context
Alp et al.[115] 2016; Turkey; 2011–13; single hospital; none	Hip and knee, deep infection, treatment with DAIR (n = 9), single-stage (n = 2) and two-stage (n = 5) n = 16 Hospital stay, mean 23.5 days (range 7–120 days) (n = 654 primary hip or knee replacement comparator group)	2013; USD converted from Turkish lira; hospital accounting system	Antibiotics; laboratory tests; radiology; prosthesis; operation; bed stay; drugs, infusions	Surgeon; anaesthesiologist; infection specialist; nurses; physiotherapists; caregivers; physical therapy	Median total cost of treating infection (predominantly DAIR) including primary joint replacement US$16,999 Median cost of primary hip or knee replacement US$5937 Total hospital costs 286% higher for infected than for uncomplicated hip or knee replacement
Assmann et al.[116] 2014; Germany; 2009–12; single hospital; none	Hip, deep infection, two-stage revision n = 30 All cases Costs incurred during hospital stays (n = 114 aseptic revision comparator group)	2013; USD (converted from euros); hospital purchase prices; documented nursing services; patient records; hospital pharmacy; laboratory, radiology and physical therapy services; clinical information system; human resources department; local ICU cost	Nursing staff; laboratory tests; radiology; physiotherapy; medication; surgeon; anaesthesiologist; anaesthesia nursing; implant; materials; sterilisation; transfusions; ICU	Fixed hospital costs	Mean cost of infection treatment including additional operations to the planned two stages, US$14,380 (range US$7813–29,051) Mean cost of aseptic revision US$5487 (range US$3080–17,345) Cost of management of infection with two-stage revision 262% higher than aseptic revision

TABLE 10 Economic evaluations of revision surgery for prosthetic hip or knee infection: cost-comparison studies (continued)

Authors and year; country; recruitment dates; setting; risk-of-bias concerns	Indication; number of patients; follow-up; comparator group	Year (cost); currency; source of data	Costs included	Costs that studies state are not included	Costs with description of context
Bozic and Ries[117] 2005; USA; 2001–2; single hospital (two surgeons); none	Hip, deep infection, two-stage revision n = 29 12 months (n = 29 primary hip replacement, n = 27 aseptic loosening comparator groups)	2001–2; USD; hospital decision support cost-accounting system and outpatient billing system	Hospital costs; outpatient visits	Non-medical costs; patient and societal costs	Mean cost of infection treatment with two-stage revision including treatment of reinfection US$96,166 (SD US$60,664) Mean costs of primary hip replacement US$21,654 (SD US$4291) and treatment of aseptic loosening US$34,866 (SD US$15,547) Management of infection with two-stage revision 276% greater than treatment of aseptic loosening and 444% greater than primary hip replacement
Gow et al.[118] 2016; New Zealand; 2013–14; single hospital; none	Hip or knee (surgical site infection within 90 days of surgery), surgical procedure (median 2, range 1–4) n = 11 (9 deep infection) Costs incurred during hospital stays (n = 22 uncomplicated hip or knee replacement)	2013; NZD; Auckland District Health Board clinical costing system	Laboratory tests; allied health input; radiology; drug therapy; bed costs	Outpatient visits; primary care visits	Mean cost including first treatment and all admissions for infection NZ$61,157 (SD NZ$41,414) Mean cost of uncomplicated hip or knee replacement NZ$21,035 (SD NZ$6296) Cost of management of infection 291% greater than uncomplicated hip or knee replacement

Authors and year; country; recruitment dates; setting; risk-of-bias concerns	Indication; number of patients; follow-up; comparator group	Year (cost); currency; source of data	Costs included	Costs that studies state are not included	Costs with description of context
Haenle et al.[119] 2012; Germany; 2004–7; single hospital; none	Hip, deep infection, not single lavage debridement, surgical treatment n = 49 Costs incurred during hospital stays and reoperations (follow-up time not specified) (n = 21 primary hip replacements)	2004–7; euros; patient records from hospital information system and data from the hospital central pharmacy and control centre	Implants; laboratory tests; radiology; blood products; antibiotics; pharmaceuticals; medical supplies; operating theatre personnel; anaesthesia; ward personnel; ICU	Patient factors: production, salary and social security taxes	Mean cost for treatment of infection including additional operations €29,331 Mean cost of primary hip replacement €6264 Cost of hip replacement with subsequent treatment of infection 468% higher than primary hip replacement
Haenle et al.[120] 2012; Germany; 2004–7; single hospital; none	Knee, deep infection, not single debridement and lavage, surgical treatment n = 28 Costs incurred during hospital stays (follow-up time not specified) (n = 21 primary knee replacements)	2011; euros; health record and hospitals health information system; DRG relevant costs; federal employee tariff; hospital central controlling unit; local ICU costs	Implants; laboratory tests; radiology; blood products; antibiotics; pharmaceuticals; medical supplies; operating theatre personnel; anaesthesia; ward personnel; ICU	Patient factors: production, salary and social security taxes	Mean cost for treatment of infection including additional operations €25,194 Mean cost of primary knee replacement €6889 Cost of treating knee infection 366% greater than primary knee replacement
Kallala et al.[121] 2015; UK; 2005–12; single hospital; none	Knee, deep infection, two-stage revision n = 45 Costs incurred during hospital stays (n = 123 aseptic revision)	2005–12; GBP; patient-level information and costing system, hospital, department of finance	Implants; materials and augments; operating theatres and recovery; ward care; physiotherapy; occupational therapy; pharmacy; radiology; laboratory tests	Readmissions for complications; patient costs; societal costs	Mean cost of first treatment for infection with two-stage revision £30,011 (SD £4514) Mean cost of aseptic revision £9655 (SD £600) Cost of revision for knee infection 311% higher than aseptic revision

TABLE 10 Economic evaluations of revision surgery for prosthetic hip or knee infection: cost-comparison studies (continued)

Authors and year; country; recruitment dates; setting; risk-of-bias concerns	Indication; number of patients; follow-up; comparator group	Year (cost); currency; source of data	Costs included	Costs that studies state are not included	Costs with description of context
Kapadia et al.[122] 2014; USA; 2007–13; single hospital; none	Knee, deep infection, two-stage revision n = 21 Minimum 1 year (n = 21 primary knee replacements)	2007–13; USD; hospital financial system	Bed stay; operating room services; admission; pharmacy; laboratory tests; radiology; anaesthesia; blood transfusion; rehabilitation; consultation services; clinic visits; reoperation costs	Patient-incurred costs	Including primary surgery, mean cost of first treatment of infected knee replacement with two-stage revision and subsequent reoperations US$116,383 (range US$44,416–269,914) Mean cost of primary knee replacement US$28,250 (range US$20,454–47,957) Cost of knee replacement with subsequent two-stage treatment of infection 412% higher than primary knee replacement
Kapadia et al.[123] 2016; USA; 2007–11; single hospital; none	Hip, deep infection, two-stage revision n = 16 Minimum 1 year (n = 32 primary hip replacements)	2007–11; USD; hospital financial system	Bed stay; operating room services; admission; pharmacy; laboratory tests; radiology; anaesthesia; blood transfusion; rehabilitation; consultation services; outpatient visits; reoperation costs	Patient-incurred costs	Including primary surgery, mean cost of first treatment of infected knee replacement with two-stage revision and subsequent reoperations US$88,623 (range US$44,043–158,202) Mean cost of primary hip replacement US$25,659 (range US$13,595–48,631) Cost of hip replacement with subsequent two-stage treatment of infection 345% higher than primary hip replacement

Authors and year; country; recruitment dates; setting; risk-of-bias concerns	Indication; number of patients; follow-up; comparator group	Year (cost); currency; source of data	Costs included	Costs that studies state are not included	Costs with description of context
Klouche et al.[124] 2010; France; 2006; single hospital; none	Hip, deep infection, single- or two-stage revision n = 40 Costs incurred during hospital stays and home hospitalisation (n = 474 primary hip replacements and n = 57 aseptic revisions)	2006; euros; analytic accounting system	Preoperative; hospital stay; staff costs; prescriptions; implants; general expenses; surgical unit; anaesthesia; physiotherapy; radiology; laboratory tests; day hospital; general services; additional hospital stay and rehabilitation; antibiotic therapy; home-based hospitalisation	Social expenses	Mean cost of single or two-stage revision for infection €32,546 (SD €9587) Mean costs of primary hip replacement $9028 (SD €1924) and aseptic revision $12,409 (SD 2059) Cost of management of infection with single or two-stage revision 262% higher than aseptic revision and 361% higher than primary hip replacement
Oduwole et al.[126] 2010; Ireland; 1997–2001, 2002–6; single hospital; none	Knee, deep infection, two-stage n = 20 (2002–6) Costs incurred during hospital stays (n = 99 aseptic revisions)	Year not specified but costs adjusted for inflation; euros; insurer cost of semi-private patient; pharmacy records	Bed-cost; surgeon's fees; implant; instrumentation; radiology; blood tests; transfusion; intravenous antibiotics; other medication	Bone scans; MRI	2002–6 mean cost of treatment of infection with two-stage revision €23,113 (range €12,180–33,853) Mean cost of aseptic revision €15,174 (range €5837–24,777) Cost of two-stage treatment of knee infection 152% higher than aseptic revision

TABLE 10 Economic evaluations of revision surgery for prosthetic hip or knee infection: cost-comparison studies (continued)

Authors and year; country; recruitment dates; setting; risk-of-bias concerns	Indication; number of patients; follow-up; comparator group	Year (cost); currency; source of data	Costs included	Costs that studies state are not included	Costs with description of context
Peel et al.[130] 2013; Australia; 2008–10; single hospital; none	DAIR for hip or knee PJI n = 21 Median 19 months (IQR 14–21 months) (n = 42 primary hip or knee replacements including two aseptic revisions)	2008–10; AUD; St Vincent's Hospital, Melbourne, administrative databases	Government perspective Inpatient care (medical, nursing, operating theatre, prosthesis, ICU, CCU, allied health, medical imaging, pathology, pharmacy, hospital in the home) Total outpatient (medical, nursing, allied health, medical imaging, pathology, pharmacy) Total emergency	Patient out-of-pocket expenses	Mean cost of DAIR was AU$69,414 Mean cost of primary hip or knee replacement (includes 2/21 aseptic revisions) was AU$22,085
Rennert-May et al.[128] 2018; Canada; 2012–15; hospitals in Canadian province; none	Hip or knee, complex surgical site infection, surgical treatment n = 258 12 months (n = 24,409 primary hip or knee replacement)	2016; CAD; Alberta health services microcosting	Admission; hospitalisation; emergency room; day surgery; day medicine visits	Other physicians; outpatient antibiotics; patient costs	Mean cost of primary hip or knee replacement and subsequent infection treatment CA$70,144 (IQR CA$35,923–86,368) of which CA$14,071 (IQR CA$10,400–14,202) was initial treatment Mean cost of primary hip or knee replacement CA$13,195 (IQR CA$10,269–13,049) Cost of hip or knee replacement with treatment of subsequent infection 532% higher than primary hip or knee replacement

Authors and year; country; recruitment dates; setting; risk-of-bias concerns	Indication; number of patients; follow-up; comparator group	Year (cost); currency; source of data	Costs included	Costs that studies state are not included	Costs with description of context
Romano *et al.*[129] 2010; Italy; 2001–6; two hospitals; none	Hip, deep infection, two-stage *n* = 40 Minimum 2 years (*n* = 40 revision for aseptic loosening)	2001–6; euros; hospital administrative decision support database	Operating room equipment; implants (including bone grafts and bone substitutes); operative staff; hospital stay in surgical and rehabilitation departments; blood; pharmacy; administrative costs	Readmissions; outpatient visits and charges; patient and societal costs	Mean cost of initial infection treatment with two-stage revision €60,394 (SD €15,886) Mean cost of aseptic revision €27,194 (SD €5122) Cost of two-stage treatment of hip infection 222% higher than aseptic revision
Vanhegan *et al.*[55] 2012; UK; 1999–2008; single hospital; none	Hip, deep infection, single or two-stage *n* = 76 Costs incurred during hospital stays (*n* = 194 aseptic revisions)	2007–8; GBP; hospital costs – methods not described	Hospital stay; surgery time; inpatient nursing; blood loss; laboratory tests; radiology; drugs; implant; materials and augmentation; operating theatre; recovery room; physiotherapy; occupational therapy	Surgeon fees; readmissions; other direct and indirect patient and societal costs	Mean cost of initial treatment of infection with two-stage revision £21,937 (SD £10,965) Mean cost of aseptic revision £11,897 (SD £4629) Cost of two-stage treatment of hip infection 184% higher than aseptic revision

AUD, Australian dollars; CAD, Canadian dollars; CCU, critical care unit; DRG, diagnosis-related group; GBP, Great British pounds; ICU, intensive care unit; MRI, magnetic resonance imaging; NZD, New Zealand dollars; PJI, prosthetic joint infection; SD, standard deviation; USD, United States dollars.

In four studies[117,119,120,128] the revision costs of infection and any subsequent treatments relating to infection were calculated. On average, the cost of revision for infection treatment and further treatments was 4.5 times (range 3.7–5.3 times) that of primary hip or knee replacement. Only one study reported the length of follow-up.[117] In the 12 months after starting treatment of hip prosthetic joint infection with two-stage revision, costs were 4.4 times higher than those for primary hip replacement.

In two studies including costs of primary hip or knee replacement and all subsequent treatments for infection including persistent infection and reinfection after a minimum of 1 year, the costs reported were 3.5 and 4.1 times that of primary hip[123] or knee[122] replacement, respectively.

Cost of infection treatment compared with cost of aseptic revision

In seven studies,[55,116,117,121,124,126,129] a comparison was made between the costs of revision for infection and those for aseptic indications. In two studies,[55,124] patients were treated with either single- or two-stage revision, and in five studies[116,117,121,126,129] patients were treated exclusively with two-stage revision. On average, the cost of revision for infection was 2.4 times (range 1.5–3.1 times) that of revision for aseptic reasons. In the five studies[116,117,121,126,129] of patients with infection treated with two-stage revision, the cost of treatment was 2.5 times (range 1.5–3.1 times) that of aseptic revision. In two UK studies, the hospital cost of two-stage treatment of hip infection was 1.8 times greater[55] and for knee infection 3.1 times greater[121] than aseptic revision. Surgeries in the two studies were conducted between 1999 and 2008 and between 2005 and 2012, respectively.

In five studies, the cost of revision surgery was reported with no consideration of subsequent re-operations for failure of infection clearance. In these studies,[55,121,124,126,129] the cost associated with the treatment of infection was 2.3 times (range 1.5 –3.1 times) that of aseptic revision.

In five studies[55,116,117,124,129] in patients with hip replacements, the costs of revision for infection were 2.4 times (range 1.8–2.8 times) those of aseptic revision. This difference was 3.1 and 1.5 in the two studies[121,126] of patients with knee replacement.

Costs of single-stage compared with costs of two-stage revision strategies

Three studies[124,125,127] compared the costs of single- and two-stage revision strategies (*Table 11*). Two studies were conducted in Australia[125,127] and one was conducted in France.[124] Two studies[125,127] involved multiple centres and one study[124] was at a single hospital. Two studies[124,125] included patients with hip infection and one study[127] included patients with both hip and knee infection. Key issues of concern were identified for each study based on the CHEC-list. In one study,[124] the comparison of costs was between first treatments, and the effectiveness in relation to prevention of persistent infection or reinfection was not considered. In two studies, the costs of further treatments were included in cost estimates, but the numbers of patients were small in one study[127] and no information on the selection of patients for treatments was provided in either study.[125,127]

In two studies,[124,125] the cost of planned revision with no further treatment for persistent infection or reinfection using a two-stage procedure was higher than for a single-stage procedure, with two-stage revision costing 1.74 times[124] or 1.58 times[125] that of a single-stage revision.

Considering all procedures, including planned operations and those required to treat persistent infection or reinfection, the relative costs differed in two studies reporting data.[125,127] In one of the studies,[125] 3 out of 25 patients required additional treatment after single-stage revision and 1 out of 14 required additional treatment after two-stage revision. The follow-up time was not stated. Considering the additional costs associated with these procedures, the overall cost of treatment with two-stage revision was approximately 1.60 times that with single-stage revision.[125] In the other study,[127] which had a mean follow-up of 26 months (standard deviation 19 months), five out of six single-stage revisions required additional operations and the overall cost of a two-stage revision was 0.6 times that of a single-stage revision.

TABLE 11 Single-stage and two-stage revision strategies: cost-comparison studies

Authors and year; country; recruitment dates; setting; risk-of-bias concerns	Indication; number of single-stage and two-stage; follow-up	Year (cost); currency; source of data	Costs included	Costs not included	Costs with description of context
Klouche et al.[124] 2010; France; 2006; single hospital; purely a comparison of first treatment costs	Hip, deep infection n = 40 total Number of single- and two-stage revisions not specified Costs incurred during hospital stays and home hospitalisation	2006; euros; analytic accounting system with internal criteria	Preoperative; hospital stay; staff costs; prescriptions; implants; general expenses; surgical unit; anaesthesia; physiotherapy; radiology; laboratory tests; day hospital; general services; additional hospital stay and rehabilitation; antibiotic therapy; home-based hospitalisation	Social expenses	Mean cost of first treatment of infection: Single-stage €31,133 (SD €9733) Two-stage €54,098 (SD €12,700) Two-stage revision of infected hip replacement cost 1.74 times more than a single-stage revision
Merollini et al.[125] 2013; Australia; 2006–9; Queensland hospitals database; no information on reason for decision to perform single- or two-stage revision	Hip, deep infection within 1 year of primary hip replacement n = 25; 14 Costs incurred during hospital stays Follow-up not reported	2006–9; AUD; national hospital cost data collection	Surgery; prostheses; hospital	Antibiotics; primary care; travel; pharmaceuticals; indirect costs	Mean cost of single-stage: AU$27,006 (range AU$8957–$36,408). Additional treatments in three patients mean AU$24,357 (range AU$15,801–36,408) Mean cost of two-stage: AU$42,772 (range AU$15,801–60,870). Total treatment costs in one patient requiring further revision: AU$70,381 Cost of successful treatment by two-stage 1.58 times single-stage. Cost of first two-stage treatment and reoperations 1.60 times that of single-stage

TABLE 11 Single-stage and two-stage revision strategies: cost-comparison studies (*continued*)

Authors and year; country; recruitment dates; setting; risk-of-bias concerns	Indication; number of single-stage and two-stage; follow-up	Year (cost); currency; source of data	Costs included	Costs not included	Costs with description of context
Peel et al.[127] 2013; Australia; 2006–8; 10 hospitals; no information on reason for decision to perform single- or two-stage revision, conclusions based on small number of patients	Hip or knee, deep infection n = 6; 6 n = 108 DAIR comparator Mean 26 months (SD 19 months)	2011–12; AUD; Australian Consumer Price Index 2012; Australian Refined Diagnosis Related Group; hospital costing data; Health Purchasing Victoria; Medicare Benefit Scheme	Surgery; prostheses; hospital; home care; antibiotics	Outpatient review; pathology; radiology; non-medical and societal costs	Median cost of first treatment of infection and persistent infection AUD34,800 (5/6 single-stage required re-revision and these costs included) In multivariate model, single-stage revision and subsequent treatments for persistent infection cost 2.00 (95% CI 1.30 to 3.10) times DAIR Two-stage revision and subsequent treatments for persistent infection cost 1.20 (95% CI 0.83 to 1.73) times DAIR Estimate two-stage cost 0.6 times single-stage

AUD, Australian dollars; SD, standard deviation.

Comparison of costs associated with different spacers

Two studies[131,132] compared the costs associated with different spacers (*Table 12*). Both studies included a group with replacement of an autoclaved original femoral component. In one study this was included in the costing and, in combination with a cement spacer, the cost was about one-quarter of that when the femoral component was replaced and a polyethylene or cement spacer was used.[131] Infection rates were reported at widely different follow-up times, and it is not possible to compare rates between the groups and, thus, to determine whether or not the cost saving was associated with differences in reinfection. The autoclaving of components, particularly without sonication, is not believed to eradicate biofilm such that it can be used in contemporary practice. There was little difference in costs between polyethylene and cement spacers when the femoral component was replaced.[131,132] In a secondary analysis, the cost of homemade cement spacers was 25% of that of commercially available versions.[132] Again, follow-up rates varied between groups and no conclusion relating to reinfection rates can be drawn.

Discussion

The costs of planned revision of infection are, on average, approximately four times those of primary hip or knee replacement and 2.4 times those of aseptic revision. The costs of further treatments associated with treatment failure are highly dependent on the success rate of revision treatments in different studies, and this varied markedly in the studies we identified. Thus, in two studies with low rates of reinfection, two-stage revision was about 60–70% more costly than single-stage revision. However, in one study with a highly unfavourable reinfection rate after single-stage revision, a two-stage strategy was associated with 40% lower costs.

The studies we identified highlight the importance of knowing the clinical effectiveness of treatment strategies when assessing the costs associated with them. In the absence of randomised evaluations, in systematic reviews of effectiveness of revision strategies for treatment of prosthetic joint infection, an attempt to limit this has been to select and compare pure case-series in which all patients with infection have received a specific treatment.[47,86,87,133] The inclusion of studies with patients selected for a treatment strategy based on infection severity or their health may give misleading results. However, as surgeons must to some degree tailor surgical management to individual patients, this may not always be avoidable. Only through the collection of detailed cost data in randomised evaluations and treatment comparisons in large unselected cohorts can definitive information on the costs and cost-effectiveness of different treatment strategies be generated.

The treatment of infection after hip and knee replacement with a two-stage revision is costly, and the single-stage revision strategy and other alternatives potentially address the need of patients and health-care providers for a less invasive, time-consuming and expensive treatment for infection. Much emphasis has been placed on the use of DAIR as an alternative to single- or two-stage revision. This is less invasive, but overall infection clearance rates may be only 61.4%, with a wide variation in rates reported in case series (range of clearance rates 11.1–100%).[85] Another option for hip infection relies on the use of a CUMARS, with the option of postponing the second stage and retaining the CUMARS prosthesis.[46] As with DAIR, this is not the final treatment for many patients, but in a case series 45% of patients receiving this treatment chose to keep the temporary prosthesis rather than receive a new prosthesis in a second-stage operation.[46] The initial costs of DAIR and a CUMARS are lower than those of a two-stage revision but, with the need for further treatments, costs may, ultimately, be higher.

In the three studies we identified comparing single- and two-stage revision and considering the financial consequences of treatment failure, the rates of successful treatment differed markedly between studies. This led to contradictory conclusions that both the single-stage and the two-stage strategy are the lower-cost option. However, in these studies the numbers of patients receiving treatment were small.

TABLE 12 Different features of revision surgery: cost-comparison studies

Authors and year; country; recruitment dates; setting	Indication; number of different features	Year (cost); currency; source of data	Costs included	Costs not included	Costs with description of context
Kalore *et al.*[131] 2012; USA; 2001–9; two hospitals	Two-stage revision of infected TKR with use of three antibiotic eluting spacer types. Reimplantation completed AOC, *n* = 15; NFC, *n* = 16; SMC, *n* = 22	Year not specified; USD	Implants; moulds; cement; antibiotics	Indirect costs related to operative time or the need for repeat hospitalisations or surgery	Mean costs: AOC, US$932; NFC, NFC US$3589; SMC, US$3945 AOC technique 0.26 cost of NFC AOC technique 0.24 cost of SMC Mean follow-up (reinfection): AOC 73 months (33.3%); NFC 19 months (12.5%); SMC 32 months 35%)
Nodzo *et al.*[132] 2017; USA; 2005–14; single institution	Two-stage revision of infected TKR with use of three articulating antibiotic eluting spacer types. Reimplantation completed AUTOCL, *n* = 39; PREFAB, *n* = 58; MOULD, *n* = 43	Year not specified; USD	Cost of prefabricated spacer, commercial cement moulds, antibiotics added to cement, and cost of each bag of cement (off-the-shelf list pricing) Cost of a new femoral implant was calculated for the AUTOCL group as regulations do not permit reimplantation of explanted components		Mean costs: AUTOCL, US$3764; PREFAB, US$4825; MOULD, commercial US$5439; MOULD, homemade US$1341 Mean follow-up (reinfection): AUTOCL 52.4 months (20.6% infection free); PREFAB 74.9 months (17.3% infection free); MOULD 43.7 months (11.6% infection free) No significant association between spacer type and reoperation in univariable or multivariable analysis

AOC, autoclaved original femoral component with polyethylene spacer; AUTOCL, autoclaved original femoral component with intraoperatively moulded cement spacer with tobramycin; MOULD, intraoperatively moulded cement spacer, a majority with tobramycin; NFC, new femoral component with polyethylene spacer; PREFAB, commercially available prefabricated polymethylmethacrylate spacer with gentamicin; SMC, new femoral component and cement spacer formed using silicone mould component; TKR, total knee replacement.

With the reporting of ongoing RCTs comparing single- and two-stage revision of joints affected by prosthetic joint infection,[97,134,135] associated economic analyses will provide both robust standalone data and information to populate decision models. Such analyses should be from a patient and societal perspective in addition to a health-care provider perspective. Until then, it is important that health-care providers are aware that the costs of treatment of prosthetic joint infection are high and vary considerably between individual patients, and that prior to the INFORM RCT, insufficient high-quality evidence was available to advise on choice of revision strategy.

Appendix 3 Literature search terms for risk factors for prosthetic joint infection as applied in MEDLINE on 1 September 2015 and described in *Risk factors for prosthetic hip or knee infection*

1. prosthetic joint infection.mp. or exp Surgical Wound Infection/ (30,119)
2. prosthetic infection.mp. (294)
3. wound infection.mp. or exp Wound Infection/ (45,531)
4. exp Sepsis/or sepsis.mp. (132,792)
5. exp Surgical Wound Infection/or surgical site infection.mp. (30,357)
6. arthroplasty.mp. or exp Arthroplasty, Replacement, Knee/or exp Arthroplasty, Replacement/or exp Arthroplasty/or exp Arthroplasty, Replacement, Hip/ (54,094)
7. joint replacement.mp. (4292)
8. exp Joint Prosthesis/or joint arthroplasty.mp. (37,545)
9. exp Arthroplasty, Replacement, Hip/or total arthroplasty.mp. (18,367)
10. risk factor.mp. or exp Risk Factors/ (661,103)
11. exp Biological Markers/or exp Risk Factors/or risk marker.mp. or exp Risk/or exp Diabetes Mellitus, Type 2/ (1,584,727)
12. predictor.mp. (109,243)
13. age.mp. (6,925,632)
14. sex.mp. or exp Sex/ (603,694)
15. body mass index.mp. or exp Body Mass Index/ (142,034)
16. body weight.mp. or exp Body Weight/ (451,315)
17. socioeconomic status.mp. or exp Social Class/ (51,072)
18. exp Smoking/or smoking.mp. (202,595)
19. exp "Tobacco Use"/or exp Tobacco/or tobacco.mp. (178,015)
20. alcohol.mp. (214,043)
21. diabetes.mp. or exp Diabetes Mellitus, Type 2/or exp Diabetes Mellitus/ (438,869)
22. exp Hypertension/or hypertension.mp. (365,828)
23. comorbidity.mp. or exp Comorbidity/ (91,604)
24. rheumatoid arthritis.mp. or exp Arthritis, Rheumatoid/ (114,884)
25. osteoarthritis.mp. or exp Osteoarthritis, Hip/or exp Osteoarthritis/or exp Osteoarthritis, Knee/ (55,616)
26. history of joint arthroplasty.mp. (5)
27. dental procedure.mp. or exp Tooth Extraction/ (17,354)
28. steroid.mp. or exp Steroids/ (779,238)
29. anticoagulant.mp. or exp Anticoagulants/ (192,581)
30. thromboprophylaxis.mp. (2762)
31. previous surgery.mp. (3074)
32. exp Femoral Fractures/or exp Hip Fractures/or exp Femoral Neck Fractures/or previous fracture surgery.mp. (30,456)
33. revision arthroplasty.mp. (973)
34. previous prosthetic joint infection.mp. (1)
35. 1 or 2 or 3 or 4 or 5 (175,563)
36. 6 or 7 or 8 or 9 (70,471)

37. 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 (9,860,110)
38. 35 and 36 (3173)
39. 37 and 38 (2441)
40. limit 39 to humans (2421)

Appendix 4 Literature search terms for hip implant fixation as a risk factor for prosthetic joint infection as applied in MEDLINE on 24 April 2019 and described in *Risk factors for prosthetic hip or knee infection*

1. exp Hip Prosthesis/ (21,604)
2. hip relacement.mp. (0)
3. exp Arthroplasty, Replacement, Hip/ (23,365)
4. exp Hip Joint/ (25,479)
5. fixation.mp. (195,733)
6. cemented.mp. (9687)
7. uncemented.mp. (2634)
8. hybrid.mp. (146,856)
9. reverse hybrid.mp. (32)
10. exp Prosthesis-Related Infections/ (10,732)
11. periprosthetic joint infection.mp. (900)
12. prosthetic joint infection.mp. (973)
13. prosthetic infection.mp. (396)
14. exp INFECTION/ (739,240)
15. exp Surgical Wound Infection/ (33,623)
16. surgical site infection.mp. (5502)
17. 1 or 2 or 3 or 4 (55,289)
18. 5 or 6 or 7 or 8 or 9 (350,215)
19. 10 or 11 or 12 or 13 or 14 or 15 or 16 (741,846)
20. 17 and 18 and 19 (466)
21. limit 20 to humans (457)

Appendix 5 Literature search terms for knee implant fixation as a risk factor for prosthetic joint infection as applied in MEDLINE in November 2018 and described in *Risk factors for prosthetic hip or knee infection*

1. exp Knee Prosthesis/ (10,710)
2. exp Arthroplasty, Replacement, Knee/ (20,199)
3. exp Knee Joint/ (55,210)
4. fixation.mp. (197,432)
5. cement*.mp. (65,551)
6. uncemented.mp. (2661)
7. hybrid.mp. (149,302)
8. reverse hybrid.mp. (33)
9. stem.mp. (416,609)
10. exp Prosthesis-Related Infections/ (10,888)
11. prosthetic joint infection.mp. (1011)
12. prosthetic infection.mp. (399)
13. exp Wound Infection/ (44,055)
14. deep infection.mp. (2795)
15. exp SEPSIS/ (113,415)
16. surgical site infection*.mp. (8323)
17. 1 or 2 or 3 (72,671)
18. 4 or 5 or 6 or 7 or 8 or 9 (811,858)
19. 10 or 11 or 12 or 13 or 14 or 15 or 16 (170,789)
20. 17 and 18 and 19 (534)
21. limit 20 to humans (529).

Appendix 6 Incidence rate ratios of revision for hip prosthetic joint infection and 95% credible intervals for patient characteristics as described in *Risk factors for prosthetic hip or knee infection*

Characteristic	Total		≤ 3 months		3–6 months		6–12 months		12–24 months		≥ 24 months	
	IRR (95% CrI)	ESS	IRR (95% CrI)	ESS	IRR (95% CrI)	ESS	IRR (95% CrI)	ESS	IRR (95% CrI)	ESS	IRR (95% CrI)	ESS
Sex												
Male	1.68 (1.56 to 1.81)	6426	1.72 (1.39 to 2.10)	4469	2.59 (1.93 to 3.44)	3170	1.93 (1.57 to 2.37)	3809	1.73 (1.47 to 2.03)	4039	1.44 (1.28 to 1.62)	4534
Female	Ref.		Ref.		Ref.		Ref.		Ref.		Ref.	
Age group (years)												
≥ 80	0.66 (0.56 to 0.76)	6519	1.42 (0.98 to 1.99)	2256	0.63 (0.32 to 1.10)	3765	0.41 (0.25 to 0.63)	4464	0.68 (0.49 to 0.91)	4120	0.48 (0.37 to 0.61)	5835
70–79	0.73 (0.66 to 0.81)	4157	0.97 (0.70 to 1.30)	2027	1.26 (0.84 to 1.82)	1896	0.67 (0.49 to 0.89)	2551	0.69 (0.55 to 0.86)	2803	0.64 (0.54 to 0.74)	3295
60–69	0.90 (0.81 to 0.99)	4255	1.14 (0.84 to 1.52)	2109	1.05 (0.69 to 1.54)	2129	1.11 (0.85 to 1.43)	2434	0.93 (0.75 to 1.14)	2809	0.76 (0.66 to 0.88)	3444
< 60	Ref.		Ref.		Ref.		Ref.		Ref.		Ref.	
Ethnicity												
Black African origin	0.80 (0.41 to 1.33)	16,984	0.00 (0.00 to 0.00)	0	0.99 (0.03 to 3.68)	18,731	0.49 (0.01 to 1.82)	18,739	0.57 (0.07 to 1.59)	18,497	1.23 (0.53 to 2.26)	17,161
Other or mixed	0.88 (0.48 to 1.40)	17,820	0.00 (0.00 to 0.00)	0	3.62 (0.98 to 8.04)	17,595	1.74 (0.47 to 3.86)	17,841	0.27 (0.01 to 1.00)	18,615	0.75 (0.25 to 1.56)	17,979
South Asian	0.70 (0.25 to 1.36)	17,463	0.98 (0.02 to 3.62)	18,738	1.70 (0.04 to 6.36)	18,959	0.00 (0.00 to 0.00)	0	1.02 (0.12 to 2.87)	18,140	0.56 (0.07 to 1.57)	18,580
Unknown	0.25 (0.16 to 0.36)	17,484	0.43 (0.14 to 0.90)	17,917	0.31 (0.04 to 0.87)	18,126	0.23 (0.05 to 0.55)	17,890	0.23 (0.08 to 0.48)	17,986	0.21 (0.10 to 0.36)	17,722
White	Ref.		Ref.		Ref.		Ref.		Ref.		Ref.	
BMI (kg/m²)												
≥ 30	1.92 (1.72 to 2.15)	1885	2.99 (2.12 to 4.13)	842	2.41 (1.51 to 3.75)	942	1.54 (1.14 to 2.04)	1357	1.99 (1.56 to 2.53)	1159	1.72 (1.45 to 2.03)	1329
25–29.9	1.25 (1.11 to 1.40)	2141	1.57 (1.09 to 2.22)	1040	1.67 (1.03 to 2.61)	1058	0.88 (0.64 to 1.19)	1673	1.31 (1.01 to 1.68)	1274	1.25 (1.05 to 1.49)	1506
< 25	Ref.		Ref.		Ref.		Ref.		Ref.		Ref.	
ASA grade												
3–5	1.63 (1.42 to 1.87)	3434	2.40 (1.57 to 3.55)	999	2.38 (1.26 to 4.15)	975	2.43 (1.65 to 3.48)	1452	1.64 (1.21 to 2.16)	1980	1.12 (0.89 to 1.37)	3620
2	1.26 (1.14 to 1.40)	2211	1.64 (1.14 to 2.32)	772	2.30 (1.38 to 3.73)	685	1.49 (1.08 to 2.03)	1029	1.25 (0.99 to 1.57)	1306	1.04 (0.89 to 1.20)	1954
1	Ref.		Ref.		Ref.		Ref.		Ref.		Ref.	
Chronic pulmonary disease	1.22 (1.08 to 1.37)	14,760	1.41 (1.03 to 1.86)	14,084	1.03 (0.62 to 1.55)	14,798	1.28 (0.92 to 1.71)	14,661	1.32 (1.03 to 1.65)	14,179	0.96 (0.77 to 1.18)	15,769
Diabetes	1.35 (1.18 to 1.54)	15,265	1.53 (1.09 to 2.07)	14,401	1.60 (1.01 to 2.35)	14,781	1.52 (1.07 to 2.07)	14,680	1.32 (0.99 to 1.71)	14,937	1.00 (0.78 to 1.27)	16,011
Dementia	1.85 (0.89 to 3.18)	17,999	3.78 (1.21 to 7.81)	17,553	1.80 (0.04 to 6.68)	18,665	2.32 (0.28 to 6.51)	18,082	0.66 (0.02 to 2.45)	19,173	0.60 (0.02 to 2.22)	18,863
Liver disease	2.35 (1.66 to 3.17)	17,138	2.24 (0.81 to 4.38)	17,260	1.39 (0.17 to 3.88)	17,992	2.52 (1.01 to 4.75)	17,781	1.90 (0.82 to 3.45)	18,270	2.43 (1.35 to 3.82)	17,701
Congestive heart failure	1.45 (1.09 to 1.86)	16,891	1.65 (0.86 to 2.71)	16,691	0.00 (0.00 to 0.00)	0	2.34 (1.26 to 3.77)	16,811	1.27 (0.67 to 2.07)	17,427	1.27 (0.74 to 1.93)	17,345

Characteristic	Total		≤ 3 months		3–6 months		6–12 months		12–24 months		≥ 24 months	
	IRR (95% CrI)	ESS	IRR (95% CrI)	ESS	IRR (95% CrI)	ESS	IRR (95% CrI)	ESS	IRR (95% CrI)	ESS	IRR (95% CrI)	ESS
Connective tissue-rheumatologic disease	1.37 (1.12 to 1.64)	16,585	1.49 (0.88 to 2.28)	16,615	2.28 (1.22 to 3.72)	15,762	1.60 (0.94 to 2.43)	16,681	1.14 (0.71 to 1.67)	16,701	1.12 (0.79 to 1.51)	16,969
Cancer												
Cancer	1.12 (0.89 to 1.37)	17,263	1.01 (0.53 to 1.66)	16,623	1.14 (0.49 to 2.11)	16,767	0.95 (0.47 to 1.61)	17,302	0.95 (0.56 to 1.46)	16,929	1.22 (0.84 to 1.67)	17,255
Metastatic	1.81 (1.07 to 2.74)	18,011	0.81 (0.10 to 2.26)	18,367	1.85 (0.22 to 5.20)	18,293	2.21 (0.60 to 4.86)	17,883	1.53 (0.42 to 3.38)	17,742	1.82 (0.66 to 3.55)	18,064
None	Ref.		Ref.		Ref.		Ref.		Ref.		Ref.	
Cerebrovascular disease	0.94 (0.65 to 1.27)	17,637	1.45 (0.68 to 2.52)	17,183	0.87 (0.18 to 2.11)	17,671	1.22 (0.49 to 2.31)	17,928	0.62 (0.23 to 1.22)	17,852	0.71 (0.34 to 1.21)	17,492
Myocardial infarction	0.99 (0.75 to 1.26)	16,677	1.17 (0.60 to 1.95)	16,958	0.53 (0.11 to 1.28)	17,940	0.65 (0.23 to 1.27)	17,265	1.14 (0.64 to 1.78)	17,442	1.00 (0.63 to 1.46)	17,532
Paraplegia and hemiplegia	1.62 (0.88 to 2.57)	17,787	0.70 (0.02 to 2.60)	18,874	2.78 (0.33 to 7.80)	18,227	1.51 (0.18 to 4.19)	18,511	2.32 (0.74 to 4.81)	16,973	1.18 (0.32 to 2.58)	18,295
Peptic ulcer disease	1.12 (0.76 to 1.54)	17,487	1.16 (0.37 to 2.40)	17,851	0.88 (0.11 to 2.49)	17,934	1.53 (0.55 to 2.99)	17,734	0.76 (0.24 to 1.55)	18,008	1.20 (0.66 to 1.92)	17,854
Peripheral vascular disease	1.19 (0.87 to 1.55)	17,278	1.25 (0.57 to 2.23)	17,575	1.01 (0.27 to 2.24)	17,968	1.76 (0.86 to 2.97)	16,949	0.87 (0.40 to 1.54)	17,734	1.00 (0.54 to 1.60)	17,477
Renal disease	1.12 (0.84 to 1.45)	17,256	1.21 (0.65 to 1.95)	16,478	1.70 (0.76 to 3.05)	16,088	0.93 (0.40 to 1.70)	17,527	0.62 (0.28 to 1.10)	17,310	0.97 (0.53 to 1.55)	17,244

CrI, credible interval; ESS, effective sample size; IRR, incidence rate ratio adjusted for age, sex, BMI and ASA grade; ref., reference.

Appendix 7 Incidence rate ratios of revision for hip prosthetic joint infection and 95% credible intervals for surgical characteristics as described in *Risk factors for prosthetic hip or knee infection*

Characteristic	Total		≤ 3 months		3–6 months		6–12 months		12–24 months		≥ 24 months	
	IRR (95% CrI)	ESS	IRR (95% CrI)	ESS	IRR (95% CrI)	ESS	IRR (95% CrI)	ESS	IRR (95% CrI)	ESS	IRR (95% CrI)	ESS
Osteoarthritis	0.69 (0.60 to 0.79)	927	0.67 (0.47 to 0.94)	756	0.49 (0.32 to 0.75)	935	0.57 (0.41 to 0.77)	868	0.79 (0.59 to 1.05)	589	0.80 (0.66 to 1.03)	523
Fractured neck of femur	1.82 (1.40 to 2.30)	16,934	3.00 (1.82 to 4.49)	4997	2.07 (0.81 to 3.94)	5272	1.38 (0.62 to 2.46)	5800	1.32 (0.70 to 2.14)	5787	1.30 (0.71 to 2.00)	6067
Previous hip infection	6.69 (4.18 to 9.80)	17,591	6.71 (1.38 to 16.31)	10,601	23.3 (7.38 to 48.63)	9769	6.45 (1.31 to 15.75)	10,766	6.92 (2.25 to 14.28)	10,718	4.30 (1.56 to 8.40)	10,859
Avascular necrosis	1.42 (1.16 to 1.71)	16,403	1.53 (0.84 to 2.44)	4270	1.16 (0.42 to 2.30)	4587	1.73 (1.02 to 2.66)	4397	1.42 (0.90 to 2.07)	4247	1.40 (0.99 to 1.81)	4501
Dysplasia/congenital dislocation	0.64 (0.42 to 0.90)	16,987	0.43 (0.05 to 1.21)	12,128	0.89 (0.11 to 2.50)	11,991	0.73 (0.20 to 1.61)	11,699	0.52 (0.17 to 1.08)	11,843	0.70 (0.38 to 1.09)	11,419
Inflammatory arthropathy	0.90 (0.64 to 1.21)	17,599	0.35 (0.04 to 1.00)	12,160	1.81 (0.58 to 3.79)	11,286	1.49 (0.67 to 2.64)	11,412	0.83 (0.36 to 1.51)	11,812	0.80 (0.48 to 1.31)	11,645
Surgical approach												
Lateral	1.32 (1.21 to 1.43)	5437	1.08 (0.86 to 1.35)	2408	1.56 (1.16 to 2.06)	2197	1.51 (1.21 to 1.87)	2027	1.53 (1.28 to 1.81)	1937	1.30 (1.16 to 1.50)	1820
Other	1.48 (1.22 to 1.77)	12,851	1.33 (0.79 to 2.03)	4412	1.20 (0.53 to 2.18)	4890	1.39 (0.80 to 2.16)	4689	1.32 (0.85 to 1.89)	4569	1.60 (1.15 to 2.06)	4593
Posterior	Ref.		Ref.		Ref.		Ref.		Ref.		Ref.	
Procedure												
Resurfacing	0.56 (0.46 to 0.67)	5451	0.68 (0.30 to 1.25)	3296	0.32 (0.11 to 0.67)	4234	0.39 (0.20 to 0.65)	3366	0.53 (0.35 to 0.76)	2445	0.70 (0.51 to 0.83)	1674
THR uncemented	0.92 (0.83 to 1.01)	3268	1.56 (1.17 to 2.05)	986	0.67 (0.48 to 0.93)	1894	0.66 (0.51 to 0.85)	1601	0.79 (0.64 to 0.96)	1408	0.90 (0.79 to 1.06)	1351
THR other	0.87 (0.77 to 0.98)	6898	1.60 (1.17 to 2.14)	1720	0.61 (0.39 to 0.90)	3829	0.95 (0.70 to 1.25)	2824	0.60 (0.45 to 0.77)	3287	0.80 (0.65 to 0.95)	2870
THR cemented	Ref.		Ref.		Ref.		Ref.		Ref.		Ref.	
Type of bearing												
MoM	1.07 (0.95 to 1.21)	3751	0.72 (0.45 to 1.08)	5077	0.42 (0.21 to 0.72)	6325	0.73 (0.49 to 1.02)	4084	1.21 (0.93 to 1.54)	2898	1.40 (1.21 to 1.69)	2035
CoP	0.82 (0.71 to 0.95)	10,206	1.08 (0.74 to 1.50)	6672	0.61 (0.34 to 0.96)	8286	0.97 (0.69 to 1.30)	6081	0.72 (0.53 to 0.96)	7474	0.70 (0.52 to 0.85)	8093
CoC	0.76 (0.66 to 0.86)	6054	1.21 (0.87 to 1.63)	3171	0.78 (0.50 to 1.16)	3893	0.64 (0.45 to 0.87)	4268	0.77 (0.59 to 0.99)	3791	0.60 (0.43 to 0.69)	5446
MoC/CoM	1.88 (1.13 to 2.83)	15,921	0.79 (0.02 to 2.95)	12,309	1.11 (0.03 to 4.16)	12,374	1.86 (0.38 to 4.55)	11,499	1.45 (0.39 to 3.25)	11,423	2.60 (1.26 to 4.38)	10,362
Other	0.98 (0.74 to 1.25)	16,134	1.81 (0.91 to 3.05)	10,400	1.11 (0.36 to 2.33)	11,201	1.33 (0.63 to 2.32)	10,688	0.92 (0.46 to 1.56)	11,505	0.80 (0.49 to 1.18)	11,183
MoP	Ref.		Ref.		Ref.		Ref.		Ref.		Ref.	

Characteristic	Total		≤ 3 months		3–6 months		6–12 months		12–24 months		≥ 24 months	
	IRR (95% CrI)	ESS	IRR (95% CrI)	ESS	IRR (95% CrI)	ESS	IRR (95% CrI)	ESS	IRR (95% CrI)	ESS	IRR (95% CrI)	ESS
General anaesthesia	1.08 (0.99 to 1.18)	5106	1.05 (0.83 to 1.30)	3932	1.27 (0.95 to 1.67)	4362	1.20 (0.97 to 1.48)	3978	1.00 (0.84 to 1.18)	4171	1.10 (0.97 to 1.25)	3318
Nerve block anaesthesia	0.97 (0.85 to 1.10)	13,240	1.14 (0.80 to 1.55)	8668	1.15 (0.72 to 1.71)	9899	0.81 (0.54 to 1.14)	10,363	1.02 (0.77 to 1.32)	9375	0.90 (0.76 to 1.13)	9311
Epidural anaesthesia	0.96 (0.84 to 1.08)	13,413	0.92 (0.61 to 1.31)	9805	1.20 (0.72 to 1.82)	9981	1.33 (0.94 to 1.80)	9818	1.05 (0.78 to 1.35)	9695	1.00 (0.80 to 1.16)	9135
Spinal anaesthesia	0.93 (0.86 to 1.01)	5365	0.88 (0.71 to 1.10)	3698	0.77 (0.57 to 1.01)	4611	0.95 (0.76 to 1.16)	3771	0.96 (0.81 to 1.13)	3556	0.90 (0.79 to 1.01)	3953
Thromboprophylaxis regime												
Not chemical	0.96 (0.84 to 1.09)	9422	0.85 (0.54 to 1.24)	8245	1.17 (0.71 to 1.76)	9633	1.25 (0.87 to 1.70)	8786	1.31 (0.99 to 1.68)	7667	1.00 (0.83 to 1.20)	6879
Chemical	Ref.		Ref.		Ref.		Ref.		Ref.		Ref.	
Acetabulum bone graft	1.08 (0.89 to 1.29)	16,221	0.75 (0.37 to 1.27)	17,111	1.41 (0.69 to 2.40)	16,596	1.50 (0.92 to 2.22)	16,483	1.10 (0.71 to 1.57)	16,893	1.00 (0.71 to 1.29)	16,435
Femur bone graft	1.84 (1.29 to 2.50)	16,220	2.35 (0.84 to 4.66)	17,330	0.66 (0.02 to 2.47)	18,866	2.09 (0.76 to 4.12)	16,726	2.46 (1.21 to 4.17)	16,903	1.50 (0.81 to 2.40)	16,899
Intraoperative event	1.48 (1.06 to 1.98)	17,144	1.93 (0.82 to 3.52)	17,661	1.40 (0.29 to 3.40)	18,255	2.08 (0.93 to 3.72)	16,578	1.62 (0.80 to 2.73)	17,208	1.00 (0.48 to 1.64)	17,696

CoC, ceramic on ceramic; CoM, ceramic on metal; CoP, ceramic on polyethylene; CrI, 95% credible interval; ESS, effective sample size; IRR, incidence rate ratio adjusted for age, sex, BMI and ASA grade; MoC, metal on polyethylene; MoM, metal on metal; MoP, metal on polyethylene; ref., reference; THR, total hip replacement.
Other = a combination of unclassifiable components.

Appendix 8 Incidence rate ratios of revision for hip prosthetic joint infection and 95% credible intervals for health system characteristics as described in *Risk factors for prosthetic hip or knee infection*

Characteristic	Total IRR (95% CrI)	ESS	≤ 3 months IRR (95% CrI)	ESS	3–6 months IRR (95% CrI)	ESS	6–12 months IRR (95% CrI)	ESS	12–24 months IRR (95% CrI)	ESS	≥ 24 months IRR (95% CrI)	ESS
Place of surgery												
Wales	1.04 (0.80 to 1.33)	4126	1.07 (0.54 to 1.88)	3496	0.91 (0.43 to 1.60)	9274	0.76 (0.41 to 1.24)	7665	1.37 (0.89 to 1.98)	4454	1.03 (0.73 to 1.39)	4541
England	Ref.		Ref.		Ref.		Ref.		Ref.		Ref.	
Funding												
Independent	0.88 (0.77 to 0.99)	8853	0.94 (0.64 to 1.31)	3396	1.10 (0.70 to 1.60)	4391	1.19 (0.87 to 1.58)	3711	0.83 (0.63 to 1.07)	4023	0.81 (0.67 to 0.97)	3396
Unspecified	0.98 (0.83 to 1.15)	13,160	0.39 (0.15 to 0.75)	5600	1.10 (0.49 to 1.98)	5463	1.49 (0.91 to 2.24)	5148	1.37 (0.95 to 1.88)	4676	1.19 (0.95 to 1.46)	4247
NHS	Ref.		Ref.		Ref.		Ref.		Ref.		Ref.	
Grade of operating surgeon												
Other	1.08 (0.96 to 1.20)	11,347	1.03 (0.76 to 1.36)	7753	1.10 (0.73 to 1.56)	8728	1.18 (0.88 to 1.54)	8516	1.25 (1.00 to 1.54)	7636	1.02 (0.85 to 1.20)	8148
Consultant	Ref.											
Consultant involved												
None involved	1.04 (0.91 to 1.19)	12,165	0.94 (0.64 to 1.32)	8500	0.94 (0.55 to 1.46)	10,075	1.02 (0.69 to 1.43)	9460	1.25 (0.95 to 1.60)	8457	1.07 (0.87 to 1.30)	8431
Assisting	1.13 (0.95 to 1.33)	14,681	1.19 (0.75 to 1.74)	9795	1.38 (0.75 to 2.22)	10,407	1.47 (0.95 to 2.11)	10096	1.26 (0.90 to 1.71)	9911	0.92 (0.68 to 1.20)	10,403
Operating	Ref.		Ref.		Ref.		Ref.		Ref.		Ref.	
Total volume: operating surgeon[a]												
> 114	0.87 (0.77 to 0.98)	5413	1.04 (0.75 to 1.39)	3123	0.64 (0.41 to 0.94)	4268	0.72 (0.53 to 0.97)	3734	0.69 (0.54 to 0.87)	3905	0.88 (0.73 to 1.05)	3822
64–114	0.86 (0.77 to 0.96)	5589	0.78 (0.56 to 1.04)	3580	0.77 (0.51 to 1.11)	4083	0.85 (0.63 to 1.11)	3491	0.74 (0.59 to 0.92)	3931	0.86 (0.73 to 1.02)	4144
29–63	1.02 (0.92 to 1.13)	5476	1.04 (0.78 to 1.35)	3432	0.97 (0.67 to 1.37)	3733	0.89 (0.67 to 1.16)	3806	0.88 (0.71 to 1.08)	3910	1.08 (0.93 to 1.25)	3714
≤ 28	Ref.											
Total volume: surgeon in charge[a]												
> 148	1.00 (0.89 to 1.12)	5163	1.13 (0.83 to 1.50)	3130	0.69 (0.45 to 1.02)	4259	1.01 (0.73 to 1.36)	2856	0.75 (0.58 to 0.94)	3688	1.01 (0.84 to 1.19)	3698
85–148	0.93 (0.83 to 1.04)	5403	0.85 (0.63 to 1.13)	3652	0.72 (0.48 to 1.05)	4226	1.13 (0.83 to 1.50)	2717	0.92 (0.73 to 1.14)	3438	0.83 (0.70 to 0.98)	4222
42–84	0.97 (0.87 to 1.07)	5748	0.84 (0.62 to 1.11)	3843	0.95 (0.65 to 1.33)	3833	1.18 (0.88 to 1.56)	2801	0.83 (0.66 to 1.03)	3688	0.96 (0.82 to 1.12)	3974
≤ 41	Ref.		Ref.		Ref.		Ref.		Ref.		Ref.	
Total volume: hospital[a]												
> 406	1.28 (1.10 to 1.48)	2830	1.91 (1.26 to 2.81)	1301	1.19 (0.79 to 1.74)	2845	1.01 (0.73 to 1.37)	2716	0.88 (0.66 to 1.15)	2516	1.12 (0.90 to 1.37)	2737
257–406	1.03 (0.90 to 1.16)	4096	1.57 (1.09 to 2.22)	1516	0.90 (0.59 to 1.31)	3361	0.74 (0.54 to 0.99)	3665	0.86 (0.67 to 1.09)	3052	0.89 (0.73 to 1.06)	4217
144–256	1.01 (0.90 to 1.13)	4592	1.23 (0.86 to 1.72)	1916	0.76 (0.49 to 1.13)	3604	0.72 (0.53 to 0.96)	3951	0.95 (0.75 to 1.19)	3252	1.01 (0.86 to 1.18)	3784
≤ 143	Ref.		Ref.		Ref.		Ref.		Ref.		Ref.	

CrI, credible interval; ESS, effective sample size; IRR, incidence rate ratio adjusted for age, sex, BMI and ASA grade; ref., reference.
a   Volume is the total number of hip replacements performed in the previous 12 months.

Appendix 9 Incidence rate ratios of revision for knee prosthetic joint infection and 95% credible intervals for patient characteristics as described in *Risk factors for prosthetic hip or knee infection*

Characteristic	Total			≤ 3 months			3–6 months			6–12 months			12–24 months			≥ 24 months		
	IRR (95% CrI)	p-value	Adjusted p-value	IRR (95% CrI)	p-value	Adjusted p-value	IRR (95% CrI)	p-value	Adjusted p-value	IRR (95% CrI)	p-value	Adjusted p-value	IRR (95% CrI)	p-value	Adjusted p-value	IRR (95% CrI)	p-value	Adjusted p-value
Sex																		
Male	1.83 (1.71 to 1.96)	< 0.0001	< 0.0001	2.37 (1.81 to 3.06)	< 0.0001	< 0.0001	2.17 (1.65 to 2.81)	< 0.0001	< 0.0001	2.19 (1.86 to 2.57)	< 0.0001	< 0.0001	1.85 (1.62 to 2.09)	< 0.0001	< 0.0001	1.57 (1.42 to 1.74)	< 0.0001	< 0.0001
Female	Ref.			Ref.			Ref.			Ref.			Ref.			Ref.		
Age (years)																		
≥ 80	0.50 (0.43 to 0.57)	< 0.0001	< 0.0001	1.85 (1.14 to 2.85)	0.01	0.05	0.64 (0.38 to 0.99)	0.05	0.16	0.57 (0.40 to 0.77)	< 0.0001	< 0.0001	0.48 (0.36 to 0.62)	< 0.0001	< 0.0001	0.32 (0.25 to 0.40)	< 0.0001	< 0.0001
70–79	0.65 (0.60 to 0.72)	< 0.0001	< 0.0001	1.11 (0.73 to 1.63)	0.69	0.87	0.70 (0.49 to 0.98)	0.04	0.14	0.71 (0.56 to 0.88)	< 0.0001	0.01	0.75 (0.62 to 0.89)	< 0.0001	0.01	0.56 (0.49 to 0.64)	< 0.0001	< 0.0001
60–69	0.76 (0.69 to 0.83)	< 0.0001	< 0.0001	1.09 (0.72 to 1.59)	0.76	0.90	0.61 (0.42 to 0.86)	0.01	0.03	0.85 (0.68 to 1.05)	0.13	0.31	0.87 (0.73 to 1.03)	0.10	0.26	0.69 (0.60 to 0.78)	< 0.0001	< 0.0001
< 60	Ref.			Ref.			Ref.			Ref.			Ref.			Ref.		
Ethnicity																		
Black African origin	1.67 (1.24 to 2.17)	< 0.0001	< 0.0001	1.70 (0.35 to 4.20)	0.58	0.79	2.05 (0.55 to 4.60)	0.28	0.54	1.47 (0.63 to 2.69)	0.38	0.63	1.79 (0.99 to 2.82)	0.06	0.17	1.64 (1.02 to 2.41)	0.03	0.12
Other and mixed	1.17 (0.84 to 1.57)	0.36	0.61	1.43 (0.29 to 3.49)	0.78	0.91	0.88 (0.10 to 2.48)	0.62	0.81	1.59 (0.75 to 2.76)	0.21	0.44	1.16 (0.57 to 1.96)	0.74	0.89	0.98 (0.53 to 1.57)	0.84	0.93
South Asian	1.17 (0.93 to 1.43)	0.17	0.38	1.51 (0.59 to 2.90)	0.41	0.65	1.89 (0.88 to 3.30)	0.09	0.23	1.14 (0.64 to 1.78)	0.72	0.88	1.33 (0.88 to 1.88)	0.18	0.39	0.91 (0.61 to 1.26)	0.54	0.75
Unclear	0.35 (0.23 to 0.48)	< 0.0001	< 0.0001	0.20 (0.01 to 0.76)	0.02	0.07	0.39 (0.05 to 1.09)	0.13	0.31	0.39 (0.14 to 0.77)	0.02	0.07	0.31 (0.12 to 0.58)	< 0.0001	0.01	0.35 (0.19 to 0.55)	< 0.0001	< 0.0001
White	Ref.			Ref.			Ref.			Ref.			Ref.			Ref.		
BMI (kg/m²)																		
≥ 30	1.46 (1.29 to 1.63)	< 0.0001	< 0.0001	2.23 (1.35 to 3.60)	0.02	0.09	1.34 (0.83 to 2.10)	0.39	0.63	1.26 (0.96 to 1.64)	0.12	0.31	1.52 (1.19 to 1.92)	< 0.0001	0.02	1.46 (1.22 to 1.73)	< 0.0001	< 0.0001
25–29.9	1.30 (1.15 to 1.46)	< 0.0001	< 0.0001	1.64 (0.96 to 2.67)	0.25	0.49	1.54 (0.94 to 2.42)	0.19	0.41	1.11 (0.84 to 1.46)	0.53	0.75	1.39 (1.08 to 1.77)	0.02	0.07	1.27 (1.05 to 1.53)	0.02	0.09
< 25	Ref.			Ref.			Ref.			Ref.			Ref.			Ref.		
ASA grade																		
3–5	1.84 (1.63 to 2.07)	< 0.0001	< 0.0001	1.85 (1.11 to 2.95)	0.02	0.08	1.89 (1.13 to 3.00)	0.02	0.07	1.80 (1.34 to 2.39)	< 0.0001	< 0.0001	1.71 (1.35 to 2.15)	< 0.0001	< 0.0001	1.76 (1.46 to 2.11)	< 0.0001	< 0.0001
2	1.23 (1.12 to 1.36)	< 0.0001	< 0.0001	1.25 (0.81 to 1.89)	0.36	0.61	1.29 (0.85 to 1.93)	0.27	0.53	1.11 (0.87 to 1.41)	0.43	0.67	1.11 (0.91 to 1.34)	0.33	0.59	1.27 (1.10 to 1.47)	< 0.0001	0.01
1	Ref.			Ref.			Ref.			Ref.			Ref.			Ref.		

Characteristic	Total IRR (95% CrI)	p-value	Adjusted p-value	≤ 3 months IRR (95% CrI)	p-value	Adjusted p-value	3–6 months IRR (95% CrI)	p-value	Adjusted p-value	6–12 months IRR (95% CrI)	p-value	Adjusted p-value	12–24 months IRR (95% CrI)	p-value	Adjusted p-value	≥ 24 months IRR (95% CrI)	p-value	Adjusted p-value
Chronic pulmonary disease	1.17 (1.05 to 1.29)	< 0.0001	0.02	1.33 (0.90 to 1.87)	0.15	0.36	1.59 (1.10 to 2.19)	0.01	0.05	1.04 (0.81 to 1.31)	0.77	0.91	1.16 (0.96 to 1.39)	0.13	0.31	1.03 (0.87 to 1.20)	0.75	0.90
Diabetes	1.35 (1.22 to 1.48)	< 0.0001	< 0.0001	0.99 (0.63 to 1.45)	0.89	0.95	1.43 (0.96 to 2.01)	0.07	0.21	1.27 (0.99 to 1.58)	0.05	0.16	1.57 (1.31 to 1.86)	< 0.0001	< 0.0001	1.17 (0.99 to 1.37)	0.06	0.18
Dementia	1.35 (0.58 to 2.43)	0.52	0.74	3.02 (0.36 to 8.52)	0.30	0.56	3.39 (0.40 to 9.51)	0.25	0.49				1.51 (0.31 to 3.64)	0.72	0.88	0.54 (0.01 to 1.99)	0.35	0.61
Liver disease	2.20 (1.60 to 2.90)	< 0.0001	< 0.0001	1.36 (0.17 to 3.83)	0.97	0.98	1.89 (0.38 to 4.59)	0.48	0.70	2.09 (0.95 to 3.70)	0.06	0.17	2.05 (1.08 to 3.31)	0.02	0.08	2.32 (1.37 to 3.51)	< 0.0001	0.01
Congestive heart failure	1.34 (1.05 to 1.68)	0.02	0.07	2.23 (1.04 to 3.90)	0.03	0.10	1.21 (0.38 to 2.51)	0.86	0.94	1.42 (0.79 to 2.25)	0.23	0.47	1.15 (0.68 to 1.75)	0.63	0.82	1.16 (0.73 to 1.69)	0.56	0.77
Rheumatologic disease	1.47 (1.27 to 1.68)	< 0.0001	< 0.0001	2.15 (1.26 to 3.31)	< 0.0001	0.02	1.95 (1.15 to 3.00)	0.01	0.04	1.27 (0.87 to 1.75)	0.22	0.44	1.33 (1.00 to 1.72)	0.05	0.15	1.40 (1.13 to 1.72)	< 0.0001	0.01
Cancer																		
Cancer	0.90 (0.73 to 1.10)	0.30	0.56	0.70 (0.25 to 1.39)	0.31	0.56	0.76 (0.27 to 1.49)	0.39	0.63	0.90 (0.54 to 1.36)	0.58	0.79	0.80 (0.52 to 1.16)	0.25	0.49	0.96 (0.68 to 1.30)	0.76	0.91
Metastatic	1.64 (0.95 to 2.50)	0.06	0.18	2.40 (0.29 to 6.77)	0.46	0.70	3.60 (0.73 to 8.74)	0.08	0.23	0.92 (0.11 to 2.55)	0.66	0.84	1.24 (0.34 to 2.72)	0.88	0.95	1.52 (0.56 to 2.95)	0.44	0.68
None	Ref.			Ref.			Ref.			Ref.			Ref.			Ref.		
Cerebrovascular disease	1.08 (0.82 to 1.37)	0.62	0.81	1.52 (0.60 to 2.88)	0.39	0.63	1.63 (0.64 to 3.08)	0.31	0.56	1.24 (0.68 to 1.98)	0.51	0.74	0.84 (0.45 to 1.33)	0.43	0.67	0.88 (0.53 to 1.33)	0.52	0.74
Myocardial infarction	1.06 (0.86 to 1.29)	0.58	0.79	1.17 (0.50 to 2.14)	0.81	0.92	0.30 (0.04 to 0.83)	0.06	0.18	1.09 (0.65 to 1.65)	0.80	0.92	1.34 (0.91 to 1.85)	0.13	0.31	0.95 (0.65 to 1.30)	0.70	0.88
Paraplegia and hemiplegia	1.59 (0.96 to 2.37)	0.06	0.18	3.59 (0.73 to 8.71)	0.08	0.23	2.35 (0.28 to 6.56)	0.47	0.70	1.78 (0.49 to 3.93)	0.40	0.65	0.88 (0.18 to 2.13)	0.63	0.82	1.45 (0.58 to 2.71)	0.45	0.69
Peptic ulcer disease	1.15 (0.86 to 1.48)	0.37	0.61	2.56 (1.09 to 4.70)	0.02	0.08	0.63 (0.08 to 1.78)	0.37	0.61	0.97 (0.42 to 1.76)	0.80	0.92	1.44 (0.85 to 2.18)	0.16	0.37	0.88 (0.51 to 1.35)	0.52	0.74
Peripheral vascular disease	1.37 (1.08 to 1.71)	0.01	0.04	0.87 (0.23 to 1.94)	0.62	0.81	1.91 (0.82 to 3.50)	0.12	0.29	1.15 (0.61 to 1.87)	0.72	0.88	1.53 (0.98 to 2.20)	0.06	0.16	1.22 (0.79 to 1.76)	0.38	0.63
Renal disease	1.26 (1.00 to 1.55)	0.04	0.14	1.23 (0.55 to 2.20)	0.68	0.86	1.22 (0.52 to 2.24)	0.73	0.89	1.13 (0.67 to 1.71)	0.70	0.88	1.31 (0.87 to 1.84)	0.18	0.40	0.90 (0.54 to 1.36)	0.58	0.79

CrI, credible interval; ESS, effective sample size; IRR, incidence rate ratio adjusted for age, sex, BMI and ASA grade; ref., reference.

Appendix 10 Incidence rate ratios of revision for knee prosthetic joint infection and 95% credible intervals for surgical characteristics as described in *Risk factors for prosthetic hip or knee infection*

Characteristic	Total IRR (95% CrI)	p-value	Adjusted p-value	≤ 3 months IRR (95% CrI)	p-value	Adjusted p-value	3–6 months IRR (95% CrI)	p-value	Adjusted p-value	6–12 months IRR (95% CrI)	p-value	Adjusted p-value	12–24 months IRR (95% CrI)	p-value	Adjusted p-value	≥ 24 months IRR (95% CrI)	p-value	Adjusted p-value
Osteoarthritis	0.66 (0.56 to 0.77)	< 0.0001	< 0.0001	0.61 (0.32 to 1.17)	0.10	0.26	0.63 (0.33 to 1.17)	0.11	0.28	0.58 (0.39 to 0.84)	< 0.0001	0.02	0.76 (0.54 to 1.07)	0.10	0.26	0.68 (0.53 to 0.87)	< 0.0001	0.01
Trauma	1.94 (1.42 to 2.55)	< 0.0001	< 0.0001	1.53 (0.18 to 4.33)	0.85	0.93	1.26 (0.15 to 3.53)	0.96	0.98	2.23 (1.01 to 3.94)	0.03	0.12	2.16 (1.15 to 3.50)	0.01	0.05	1.86 (1.13 to 2.78)	0.01	0.04
Previous knee infection	4.86 (2.71 to 7.64)	< 0.0001	< 0.0001	5.47 (0.14 to 20.34)	0.38	0.63	9.71 (1.16 to 27.27)	0.01	0.06	1.90 (0.05 to 7.04)	0.96	0.98	5.00 (1.36 to 11.03)	0.01	0.03	5.10 (2.04 to 9.52)	< 0.0001	< 0.0001
Avascular necrosis	1.56 (0.97 to 2.33)	0.06	0.17	1.15 (0.03 to 4.23)	0.73	0.89	2.33 (0.28 to 6.51)	0.48	0.70	3.15 (1.26 to 5.93)	0.01	0.04	1.47 (0.48 to 3.02)	0.55	0.77	1.03 (0.38 to 2.00)	0.89	0.95
Inflammatory arthropathy	1.38 (1.15 to 1.65)	< 0.0001	0.01	2.04 (0.91 to 3.66)	0.07	0.19	1.98 (0.93 to 3.45)	0.06	0.18	1.24 (0.71 to 1.91)	0.47	0.70	1.22 (0.79 to 1.74)	0.37	0.61	1.43 (1.09 to 1.83)	0.01	0.04
Other indication	1.36 (0.85 to 1.99)	0.19	0.40	0.82 (0.02 to 3.06)	0.54	0.75	1.45 (0.17 to 4.06)	0.90	0.96	0.57 (0.07 to 1.60)	0.31	0.56	1.18 (0.43 to 2.31)	0.86	0.94	1.84 (0.94 to 3.05)	0.06	0.18
Surgical approach																		
Lateral parapatellar	1.08 (0.79 to 1.42)	0.64	0.83	1.66 (0.44 to 3.69)	0.49	0.72	4.39 (2.16 to 7.45)	< 0.0001	< 0.0001	1.32 (0.60 to 2.34)	0.52	0.74	0.84 (0.38 to 1.48)	0.51	0.74	0.68 (0.37 to 1.09)	0.13	0.31
Midvastus	0.82 (0.64 to 1.02)	0.08	0.23	0.93 (0.33 to 1.87)	0.71	0.88	0.76 (0.24 to 1.58)	0.42	0.66	0.45 (0.19 to 0.82)	0.02	0.08	0.88 (0.56 to 1.28)	0.48	0.70	0.86 (0.59 to 1.19)	0.36	0.61
Subvastus	0.91 (0.67 to 1.19)	0.47	0.70	0.82 (0.17 to 2.01)	0.56	0.77	0.94 (0.19 to 2.28)	0.71	0.88	1.35 (0.66 to 2.28)	0.43	0.67	0.98 (0.52 to 1.59)	0.82	0.93	0.78 (0.47 to 1.18)	0.25	0.49
Other	1.01 (0.77 to 1.28)	1.00	1.00	1.02 (0.32 to 2.17)	0.85	0.93	1.16 (0.37 to 2.41)	0.93	0.97	0.96 (0.47 to 1.63)	0.77	0.91	0.98 (0.57 to 1.51)	0.84	0.93	1.00 (0.66 to 1.43)	0.92	0.97
Medial parapatellar	Ref.						Ref.			Ref.			Ref.			Ref.		
Procedure																		
TKR uncemented	0.71 (0.60 to 0.84)	< 0.0001	< 0.0001	0.94 (0.45 to 1.63)	0.72	0.88	1.56 (0.89 to 2.43)	0.11	0.27	0.62 (0.37 to 0.92)	0.03	0.10	0.86 (0.61 to 1.15)	0.30	0.56	0.55 (0.41 to 0.71)	< 0.0001	< 0.0001
TKR other	0.89 (0.66 to 1.16)	0.38	0.63	1.15 (0.23 to 2.82)	0.95	0.98	0.37 (0.01 to 1.38)	0.22	0.45	1.30 (0.61 to 2.25)	0.53	0.75	1.14 (0.63 to 1.81)	0.72	0.88	0.81 (0.51 to 1.19)	0.29	0.55
Patellofemoral	0.33 (0.19 to 0.50)	< 0.0001	< 0.0001				0.35 (0.01 to 1.30)	0.21	0.43	0.49 (0.13 to 1.09)	0.12	0.29	0.15 (0.02 to 0.43)	0.01	0.04	0.38 (0.18 to 0.68)	< 0.0001	0.02
Unicondylar	0.54 (0.46 to 0.61)	< 0.0001	< 0.0001	0.53 (0.27 to 0.88)	0.02	0.09	1.04 (0.63 to 1.55)	0.97	0.98	0.42 (0.27 to 0.60)	< 0.0001	< 0.0001	0.46 (0.33 to 0.61)	< 0.0001	< 0.0001	0.56 (0.45 to 0.68)	< 0.0001	< 0.0001
TKR cemented	Ref.			Ref.			Ref.			Ref.			Ref.			Ref.		

Characteristic	Total			≤ 3 months			3–6 months			6–12 months			12–24 months			≥ 24 months		
	IRR (95% CrI)	p-value	Adjusted p-value	IRR (95% CrI)	p-value	Adjusted p-value	IRR (95% CrI)	p-value	Adjusted p-value	IRR (95% CrI)	p-value	Adjusted p-value	IRR (95% CrI)	p-value	Adjusted p-value	IRR (95% CrI)	p-value	Adjusted p-value
Type of constraint																		
Unconstrained mobile	1.02 (0.89 to 1.17)	0.79	0.92	1.43 (0.82 to 2.24)	0.20	0.42	1.29 (0.74 to 2.00)	0.38	0.63	0.93 (0.65 to 1.27)	0.63	0.82	1.16 (0.89 to 1.47)	0.29	0.55	0.97 (0.79 to 1.17)	0.71	0.88
Posterior stabilised fixed	1.38 (1.27 to 1.50)	< 0.0001	< 0.0001	1.41 (1.01 to 1.90)	0.04	0.14	1.34 (0.96 to 1.80)	0.09	0.23	1.41 (1.16 to 1.69)	< 0.0001	0.01	1.32 (1.12 to 1.53)	< 0.0001	0.01	1.40 (1.24 to 1.59)	< 0.0001	< 0.0001
Posterior stabilised mobile	0.90 (0.67 to 1.18)	0.44	0.68	0.86 (0.17 to 2.14)	0.60	0.81	0.91 (0.18 to 2.24)	0.66	0.85	0.96 (0.43 to 1.71)	0.78	0.91	0.85 (0.44 to 1.42)	0.50	0.73	1.03 (0.67 to 1.48)	0.96	0.98
Constrained condylar	3.50 (2.52 to 4.65)	< 0.0001	< 0.0001	4.02 (1.07 to 9.02)	0.02	0.09	3.30 (0.66 to 8.11)	0.11	0.28	2.75 (1.10 to 5.20)	0.02	0.08	3.60 (1.90 to 5.87)	< 0.0001	< 0.0001	3.50 (1.99 to 5.46)	< 0.0001	< 0.0001
Fixed	0.72 (0.56 to 0.92)	0.01	0.04	1.06 (0.43 to 2.03)	0.97	0.98	1.17 (0.46 to 2.25)	0.85	0.93	0.69 (0.35 to 1.14)	0.17	0.38	0.56 (0.30 to 0.90)	0.03	0.10	0.70 (0.45 to 1.01)	0.07	0.19
Mobile	0.57 (0.48 to 0.68)	< 0.0001	< 0.0001	0.39 (0.12 to 0.83)	0.03	0.12	1.10 (0.59 to 1.80)	0.83	0.93	0.37 (0.20 to 0.59)	< 0.0001	< 0.0001	0.50 (0.34 to 0.70)	< 0.0001	< 0.0001	0.65 (0.50 to 0.81)	< 0.0001	< 0.0001
Undetermined	1.11 (0.90 to 1.33)	0.34	0.59	1.54 (0.65 to 2.86)	0.34	0.59	1.64 (0.73 to 2.96)	0.23	0.46	1.02 (0.57 to 1.60)	0.95	0.98	1.21 (0.80 to 1.70)	0.37	0.62	0.98 (0.71 to 1.30)	0.85	0.93
Unconstrained fixed	Ref.			Ref.			Ref.			Ref.			Ref.			Ref.		
General anaesthesia	1.11 (1.04 to 1.20)	< 0.0001	0.02	1.05 (0.79 to 1.36)	0.79	0.92	1.27 (0.96 to 1.63)	0.09	0.24	1.19 (1.00 to 1.40)	0.05	0.16	1.12 (0.98 to 1.28)	0.09	0.24	1.13 (1.01 to 1.25)	0.03	0.11
Nerve block anaesthesia	1.02 (0.94 to 1.11)	0.60	0.81	1.23 (0.87 to 1.67)	0.24	0.48	1.00 (0.70 to 1.37)	0.94	0.98	1.03 (0.84 to 1.26)	0.78	0.91	1.02 (0.87 to 1.20)	0.80	0.92	1.00 (0.88 to 1.14)	0.97	0.98
Epidural anaesthesia	0.89 (0.79 to 0.99)	0.04	0.14	0.55 (0.28 to 0.92)	0.03	0.12	1.06 (0.64 to 1.59)	0.90	0.96	0.82 (0.58 to 1.09)	0.18	0.39	1.03 (0.82 to 1.27)	0.83	0.93	0.99 (0.84 to 1.16)	0.88	0.95
Spinal anaesthesia	0.90 (0.84 to 0.97)	< 0.0001	0.02	1.06 (0.80 to 1.37)	0.75	0.90	0.77 (0.59 to 0.99)	0.04	0.14	0.84 (0.71 to 0.99)	0.04	0.14	0.89 (0.78 to 1.02)	0.09	0.24	0.88 (0.79 to 0.97)	0.01	0.06
Thromboprophylaxis regimen																		
Not chemical	0.88 (0.78 to 0.98)	0.02	0.09	1.00 (0.62 to 1.49)	0.92	0.97	0.96 (0.59 to 1.42)	0.75	0.90	1.02 (0.76 to 1.32)	0.95	0.98	0.96 (0.77 to 1.19)	0.70	0.88	0.93 (0.79 to 1.08)	0.33	0.59
Chemical	Ref.			Ref.			Ref.			Ref.			Ref.			Ref.		
Tibial bone graft	1.95 (1.31 to 2.71)	< 0.0001	< 0.0001	2.92 (0.60 to 7.11)	0.16	0.37	0.96 (0.02 to 3.59)	0.63	0.82	1.50 (0.41 to 3.28)	0.61	0.81	3.22 (1.72 to 5.21)	< 0.0001	< 0.0001	1.35 (0.62 to 2.38)	0.47	0.70
Femoral bone graft	1.56 (1.00 to 2.25)	0.04	0.14	1.51 (0.18 to 4.25)	0.86	0.94				0.87 (0.18 to 2.11)	0.62	0.81	1.79 (0.81 to 3.15)	0.13	0.31	1.82 (0.87 to 3.11)	0.09	0.25
Intraoperative event	1.19 (0.75 to 1.73)	0.48	0.70	2.40 (0.48 to 5.93)	0.28	0.54				1.14 (0.31 to 2.53)	1.00	1.00	1.46 (0.63 to 2.67)	0.39	0.63	0.98 (0.42 to 1.77)	0.82	0.93

CrI, credible interval; IRR, incidence rate ratio adjusted for age, sex, BMI and ASA grade; ref., reference; TKR, total knee replacement.

Appendix 11 Incidence rate ratios of revision for knee prosthetic joint infection and 95% credible intervals for health system characteristics as described in *Risk factors for prosthetic hip or knee infection*

Characteristic	Total			≤ 3 months			3–6 months			6–12 months			12–24 months			≥ 24 months		
	IRR (95% CrI)	p-value	Adjusted p-value	IRR (95% CrI)	p-value	Adjusted p-value	IRR (95% CrI)	p-value	Adjusted p-value	IRR (95% CrI)	p-value	Adjusted p-value	IRR (95% CrI)	p-value	Adjusted p-value	IRR (95% CrI)	p-value	Adjusted p-value
Place of surgery																		
Wales	0.88 (0.70 to 1.08)	0.21	0.43	1.22 (0.59 to 2.18)	0.67	0.85	0.77 (0.37 to 1.34)	0.34	0.59	0.66 (0.41 to 0.99)	0.05	0.16	0.80 (0.56 to 1.10)	0.17	0.38	1.00 (0.77 to 1.29)	0.98	0.99
England	Ref.			Ref.			Ref.			Ref.			Ref.			Ref.		
Funding																		
Independent	0.85 (0.75 to 0.95)	0.01	0.03	1.12 (0.71 to 1.64)	0.67	0.86	1.36 (0.91 to 1.92)	0.13	0.31	1.14 (0.87 to 1.46)	0.34	0.59	0.76 (0.59 to 0.96)	0.02	0.09	0.71 (0.59 to 0.85)	< 0.0001	< 0.0001
Unspecified	0.84 (0.72 to 0.97)	0.02	0.09	1.04 (0.48 to 1.84)	0.96	0.98	0.81 (0.34 to 1.49)	0.46	0.70	1.00 (0.64 to 1.44)	0.92	0.97	1.03 (0.74 to 1.38)	0.90	0.96	0.90 (0.73 to 1.09)	0.29	0.55
NHS	Ref.			Ref.			Ref.			Ref.			Ref.			Ref.		
Grade operating surgeon																		
Other	0.99 (0.90 to 1.08)	0.79	0.92	0.84 (0.55 to 1.19)	0.32	0.57	1.39 (0.99 to 1.88)	0.05	0.16	1.01 (0.80 to 1.25)	0.95	0.98	1.14 (0.95 to 1.34)	0.16	0.36	0.98 (0.85 to 1.12)	0.78	0.91
Consultant	Ref.			Ref.			Ref.			Ref.			Ref.			Ref.		
Consultant involved																		
None involved	0.96 (0.86 to 1.07)	0.47	0.70	0.67 (0.38 to 1.07)	0.11	0.27	1.33 (0.86 to 1.92)	0.20	0.41	1.08 (0.81 to 1.39)	0.62	0.81	1.14 (0.92 to 1.39)	0.22	0.44	0.96 (0.81 to 1.12)	0.56	0.77
Assisting	1.04 (0.90 to 1.19)	0.61	0.81	1.11 (0.61 to 1.76)	0.81	0.92	1.49 (0.88 to 2.30)	0.13	0.31	0.90 (0.61 to 1.26)	0.52	0.74	1.12 (0.85 to 1.44)	0.44	0.68	1.04 (0.83 to 1.27)	0.77	0.91
Operating	Ref.			Ref.			Ref.			Ref.			Ref.			Ref.		
Total volume of operating surgeon[a]																		
> 85	0.95 (0.86 to 1.04)	0.26	0.51	1.24 (0.83 to 1.78)	0.31	0.57	0.91 (0.61 to 1.29)	0.54	0.75	0.90 (0.72 to 1.12)	0.34	0.59	0.74 (0.61 to 0.88)	< 0.0001	0.01	0.86 (0.73 to 0.99)	0.04	0.14
51–85	0.96 (0.87 to 1.05)	0.34	0.59	1.23 (0.83 to 1.75)	0.33	0.59	0.86 (0.58 to 1.22)	0.37	0.61	0.99 (0.79 to 1.22)	0.85	0.93	0.78 (0.65 to 0.93)	0.01	0.03	0.88 (0.76 to 1.00)	0.06	0.18
26–50	1.09 (1.00 to 1.19)	0.05	0.16	1.25 (0.85 to 1.78)	0.28	0.54	1.18 (0.82 to 1.65)	0.41	0.65	0.81 (0.64 to 1.01)	0.06	0.19	1.00 (0.85 to 1.19)	0.99	1.00	1.14 (1.01 to 1.29)	0.04	0.14
≤ 25	Ref.			Ref.			Ref.			Ref.			Ref.			Ref.		

Characteristic	Total IRR (95% CrI)	p-value	Adjusted p-value	≤ 3 months IRR (95% CrI)	p-value	Adjusted p-value	3–6 months IRR (95% CrI)	p-value	Adjusted p-value	6–12 months IRR (95% CrI)	p-value	Adjusted p-value	12–24 months IRR (95% CrI)	p-value	Adjusted p-value	≥ 24 months IRR (95% CrI)	p-value	Adjusted p-value
Total volume of surgeon in charge[a]																		
> 110	0.96 (0.87 to 1.06)	0.46	0.70	1.21 (0.82 to 1.74)	0.37	0.61	0.88 (0.60 to 1.25)	0.45	0.69	0.94 (0.75 to 1.18)	0.57	0.79	0.78 (0.64 to 0.93)	0.01	0.03	0.88 (0.75 to 1.02)	0.08	0.23
71–110	0.99 (0.90 to 1.09)	0.84	0.93	1.13 (0.76 to 1.63)	0.58	0.79	0.98 (0.67 to 1.39)	0.84	0.93	0.99 (0.79 to 1.23)	0.88	0.95	0.89 (0.74 to 1.05)	0.17	0.38	0.86 (0.74 to 0.99)	0.03	0.12
39–70	1.02 (0.94 to 1.11)	0.64	0.83	1.29 (0.89 to 1.82)	0.19	0.41	1.04 (0.72 to 1.46)	0.88	0.95	0.90 (0.72 to 1.12)	0.34	0.59	0.86 (0.72 to 1.01)	0.07	0.19	1.04 (0.92 to 1.18)	0.52	0.74
≤ 38	Ref.			Ref.			Ref.			Ref.			Ref.			Ref.		
Total volume of hospital[a]																		
> 440	1.25 (1.10 to 1.42)	< 0.0001	0.01	2.09 (1.31 to 3.18)	< 0.0001	0.01	0.95 (0.63 to 1.37)	0.71	0.88	1.03 (0.79 to 1.32)	0.87	0.94	1.00 (0.80 to 1.23)	0.94	0.98	1.00 (0.84 to 1.19)	0.97	0.98
286–440	1.24 (1.11 to 1.37)	< 0.0001	< 0.0001	1.28 (0.82 to 1.90)	0.30	0.56	0.98 (0.66 to 1.40)	0.84	0.93	1.01 (0.79 to 1.27)	1.00	1.00	1.16 (0.95 to 1.40)	0.15	0.35	1.11 (0.96 to 1.29)	0.17	0.38
151–285	1.15 (1.04 to 1.26)	0.01	0.03	1.21 (0.79 to 1.77)	0.42	0.66	0.98 (0.67 to 1.39)	0.83	0.93	0.96 (0.76 to 1.20)	0.68	0.86	1.14 (0.94 to 1.36)	0.19	0.40	1.10 (0.96 to 1.25)	0.20	0.41
≤ 150	Ref.			Ref.			Ref.			Ref.			Ref.			Ref.		

CrI, credible interval; IRR, incidence rate ratio adjusted for age, sex, BMI and ASA grade; ref., reference.
a   Volume is the total number of knee replacements performed in the previous 12 months.

Appendix 12 Literature search terms for use of alpha-defensin and leucocyte in the diagnosis of prosthetic joint infections as applied in MEDLINE on 30 May 2015 and described in *Diagnosis of prosthetic joint infection: assessment of new methods*

1. neutrophil antimicrobial peptide.mp. or alpha-defensins/
2. alpha defensin.mp. or alpha-defensins/
3. alpha-defensins/or peptide neutrophil antimicrobial.mp.
4. beta-defensins/or defensin.mp. or alpha-defensins/or defensins/
5. Arthroplasty, replacement/or knee joint/or arthroplasty, replacement, knee/or arthroplasty, replacement, hip/or hip prosthesis/or joint replacement.mp. or joint prosthesis/
6. Arthroplasty, replacement, knee/or arthroplasty, replacement, elbow/or arthroplasty, subchondral/ or arthroplasty, replacement, ankle/or arthroplasty.mp. or arthroplasty, replacement, finger/or arthroplasty, replacement/or arthroplasty/or arthroplasty, replacement, hip/
7. Bacterial infections/or prosthesis-related infections/or prosthetic joint infection.mp. or surgical wound infection/
8. 5 or 6 or 7
9. 1 or 2 or 3 or 4
10. 8 and 9
11. leukocyte esterase.mp.
12. leucocyte esterase.mp.
13. 11 or 12
14. 8 and 13
15. 10 or 14

Appendix 13 Mortality and re-revision following single-stage and two-stage revision surgery for the management of infected primary hip or knee replacement in England and Wales as summarised in *Surgical treatment of prosthetic joint infection: evidence from cohort studies*

Introduction

We aimed to compare risk of re-revision and mortality after single- or two-stage revision procedures for treatment of hip or knee prosthetic joint infection in England and Wales.

Methods

Study design and data sources
Data for England and Wales from the NJR collected between 1 April 2003 and 31 December 2014 were linked with ONS data to provide the dates of death of patients who had died following single- or two-stage revision surgery. Patient consent was obtained for data collection and linkage by the NJR. According to the NHS Health Research Authority, separate consent and ethics approval were not required for this study.

Procedures and outcomes
We included patients with a primary hip or knee replacement that had subsequently been revised for prosthetic joint infection with a single- or two-stage procedure. NJR component-level data were used to identify the precise type of revision procedure. We considered all-cause re-revision and re-revision specifically for prosthetic joint infection.

In the mortality analysis, we compared primary hip or knee replacements with no revision, those revised for a non-septic indication and those revised for a prosthetic joint infection.

Age, sex and ASA grade at the time of the first revision for prosthetic joint infection were recorded.

Statistical methods
We compared re-revisions experienced by patients with infected primary hip or knee replacement treated with an initial single- or two-stage revision procedure using zero-truncated Poisson. Patients were followed up from the date of their first single-stage or stage one of a two-stage procedure until 31 December 2014, the date of their death or the date of a re-revision. A Kaplan–Meier failure function was produced to assess the cumulative re-revision incidence by study group. We used a Cox shared frailty model to compute the overall hazard ratio (HR) of re-revision for the first two years following single-stage revision performed for prosthetic joint infection (two-stage used as the reference). These time-averaged HRs were supplemented with time-dependent HRs to capture time-specific disparities between revision procedures. We used Poisson regression (time at risk modelled as an offset) adjusted for age, sex and ASA grade and modelled the baseline hazard function with restricted cubic splines.

We used a similar approach to compare the incidence of re-revision for prosthetic joint infection (restricted cubic splines Poisson model with two degrees of freedom) and the risk of mortality (restricted cubic splines Poisson model with three degrees of freedom) revision procedure types.

We also compared the mortality rates of patients with unrevised primary procedures and patients with primary procedures revised for a non-septic indication with the mortality rates of patients revised for prosthetic joint infection.

Results: hip revision procedures

Between 2003 and 2014, 2140 primary hip replacements were revised for prosthetic joint infection: 535 with a single-stage procedure and 1605 with a two-stage procedure. Patients revised with single-stage procedure were on average older (68 years vs. 66 years) and less likely to be male (51% vs. 55%) and to have an ASA grade of > 2 (26% vs. 29%) than patients revised with a two-stage procedure.

Number of revision surgeries performed
The two-stage group underwent more operations than those managed with a single-stage procedure (mean number of procedures 2.2 vs. 1.3). Among patients receiving a single-stage revision, 16% required more than one procedure, with 8% re-revised three to five times. In patients receiving two-stage revision, 13% required more than two procedures with 5% re-revised four to nine times.

All-cause re-revision
Of the 2140 primary hip replacements revised for prosthetic joint infection, 311 underwent re-revision for any cause. The adjusted risk of re-revision in the first two postoperative years was higher following single-stage revision than two-stage revision (HR 1.54, 95% CI 1.15 to 2.07; $p = 0.004$).

Re-revision for prosthetic joint infection
Of the re-revisions, 187 (60%) were performed for an indication of prosthetic joint infection. The adjusted risk of re-revision for prosthetic joint infection in the first two postoperative years was higher following single-stage revision than two-stage revision (HR 1.70, 95% CI 1.19 to 2.44; $p = 0.004$). The increased incidence of re-revision for prosthetic joint infection after single-stage revision was apparent mainly in the first 3 months after the revision operation.

Mortality
Three-hundred and four patients who received revision surgery for hip prosthetic joint infection died. The adjusted risk of mortality in the first 2 years was comparable between single-stage and two-stage revision (HR 1.05, 95% CI 0.68 to 1.62; $p = 0.814$). No time-specific difference was noted.

Compared with patients who had undergone a primary hip replacement, mortality at 2 years was higher following both single- and two-stage revision for prosthetic joint infection (HR 1.40, 95% CI 0.95 to 2.06, $p = 0.085$, and HR 1.48, 95% CI 1.22 to 1.76, $p < 0.001$, respectively).

Compared with patients who had undergone a revision for a non-septic indication, mortality at 2 years was not different following single-stage revision for prosthetic joint infection (HR 1.30, 95% CI 0.88 to 1.94; $p = 0.187$) but was higher following two-stage revision (HR 1.37, 95% CI 1.11 to 1.70; $p = 0.003$).

Results: knee revision procedures

Between 2003 and 2014, 3369 primary knee replacements were revised for prosthetic joint infection. Of these, 489 were treated with a single-stage procedure and 2377 with both stages of a two-stage procedure. A further 503 patients received only the first stage of a planned two-stage procedure.

Number of revision surgeries performed

The two-stage group underwent more operations than those managed with a single-stage procedure (mean number of procedures 2.2 vs. 1.2). Among patients receiving a single-stage revision, 14.3% required more than one revision procedure, with 7.5% re-revised three to five times. In patients receiving two-stage revision, 11.5% required more than two procedures, with 6% re-revised four to eight times.

All-cause re-revision

Of the 3369 primary knee replacements revised for prosthetic joint infection, 397 subsequently underwent re-revision for any cause. The analysis provided weak evidence that the risk of re-revision was higher in the first two postoperative years after single-stage than after two-stage revision (HR 1.32, 95% CI 0.97 to 1.81; $p = 0.08$) and this was mainly apparent in the first 3 months postoperatively (HR 1.51, 95% CI 0.95 to 2.41; $p = 0.08$).

Re-revision for prosthetic joint infection

Of the re-revisions, 291 (73%) were performed for an indication of prosthetic joint infection. The adjusted risk of re-revision for prosthetic joint infection in the first two postoperative years was similar between single- and two-stage revision (HR 1.09, 95% CI 0.76 to 1.57; $p = 0.66$).

Mortality

Three-hundred and sixty-nine patients who received revision surgery for knee prosthetic joint infection died. The adjusted risk of mortality in the first 2 years was comparable between single-stage and two-stage revision (HR 1.21, 95% CI 0.72 to 2.03; $p = 0.47$). There was evidence that mortality was lower between 6 and 18 months in patients who had undergone a single-stage revision.

Compared with patients who had undergone a primary knee replacement, mortality at 2 years was similar following single-stage revision for prosthetic joint infection (HR 1.37, 95% CI 0.84 to 2.23; $p = 0.21$) but higher following two-stage revision (HR 1.66, 95% CI 1.40 to 1.96; $p < 0.001$).

Compared with patients who had undergone a revision for a non-septic indication, mortality at 2 years was similar following single-stage revision for prosthetic joint infection (HR 1.40, 95% CI 0.84 to 2.31; $p = 0.19$) but higher for those who underwent a two-stage revision (HR 1.69, 95% CI 1.38 to 2.08; $p = 0.001$).

Discussion

Our study of over 2000 revisions for the management of infected primary hip replacements shows that single-stage revision is associated with a higher risk of unplanned re-revision for both all-cause and specifically for further prosthetic joint infection when compared with two-stage revision. This is particularly marked in the earlier post-operative period.

In the management of knee prosthetic joint infection with over 3000 patients studied, rates of re-revision for all causes and specifically for reinfection were similar after single- and two-stage revision procedures.

Compared with patients receiving two-stage revision, those with single-stage revision for the treatment of hip and knee prosthetic joint infection received an average of 41% and 45% fewer operations respectively.

Although mortality was higher than after primary hip replacement or aseptic revision, mortality rates were comparable between single- and two-stage revision treatments of hip prosthetic joint infection. After revision of knee prosthetic joint infection, there was a higher mortality in patients who received

a two-stage revision compared with those receiving a primary hip replacement or aseptic revision. There was no difference in mortality after single-stage revision compared with primary hip replacement or aseptic revision. Overall, mortality after single- and two-stage revision for knee prosthetic joint infection was similar.

To our knowledge, this is the largest study to compare the incidence of re-revision after single-stage and two-stage revision for prosthetic joint infection. We used a standardised data collection process and adjustment approach, examining component-level data to precisely define and group comparable procedures. Only procedures in which an implant is added, removed or modified are recorded in the NJR. Thus, we were unable to explore the risks for prosthetic joint infection treated with antibiotics or incision and drainage alone, but the reoperation outcomes are substantially worse for this strategy. The NJR does not capture data on the presence of a sinus or the microorganism causing the prosthetic joint infection and there may be selection of patients with easier to treat infections for a particular revision strategy.

Our research shows some advantage for a two-stage strategy over the single-stage revision with regard to preventing re-revision. However, with a two-stage strategy, the treatment burden for patients and families due to the greater number of surgeries, complications associated with the interim period and prolonged periods of immobility is considerable.

Appendix 14 Literature search terms for longitudinal studies of debridement, antibiotics and implant retention as applied in MEDLINE on 30 September 2017 and described in *Surgical treatment of prosthetic joint infection: evidence from cohort studies*

1. peri-prosthetic joint infection.mp. (11)
2. exp Prosthesis-Related Infections/1416, 1377, 1346, 1390, 1398 (10,156)
3. prosthetic joint infection.mp. (790)
4. peri-prosthetic infection.mp. (45)
5. deep infection.mp. (2634)
6. exp Wound Infection/1416, 1377, 1346, 1390, 1398 (42,315)
7. exp Sepsis/1416, 1377, 1346, 1390, 1398 (108,817)
8. exp Surgical Wound Infection/1416, 1377, 1346, 1390, 1398 (32,495)
9. DAIR.mp. (187)
10. exp Debridement/1416, 1377, 1346, 1390, 1398 (14,239)
11. implant retention.mp. (148)
12. exp Arthroplasty, Replacement/1416, 1377, 1346, 1390, 1398 (43,299)
13. exp Arthroplasty/1416, 1377, 1346, 1390, 1398 (54,112)
14. exp Arthroplasty, Replacement, Hip/1416, 1377, 1346, 1390, 1398 (21,936)
15. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 (160,263)
16. 9 or 10 or 11 (14,507)
17. 12 or 13 or 14 (54,112)
18. 15 and 16 and 17 (356)
19. limit 18 to humans (353)

Appendix 15 Literature search terms for longitudinal studies of hip prosthetic joint infection as applied in MEDLINE in March 2015 and described in *Surgical treatment of prosthetic joint infection: evidence from cohort studies*

1. exp Prosthesis-Related Infections/or prosthesis-related infection*.mp. or exp Sepsis/ (101,971)
2. exp Infection/or exp Wound Infection/or exp Surgical Wound Infection/or infection*.mp. (1,603,015)
3. wound infection.mp. or exp Wound Infection/ (44,687)
4. arthroplasty.mp. or exp Arthroplasty, Replacement/or exp Arthroplasty/or exp Arthroplasty, Replacement, Hip/ (52,003)
5. exp Arthroplasty, Replacement, Hip/or exp Arthroplasty, Replacement/or Replacement.mp. (204,405)
6. exp Hip/or exp Arthroplasty, Replacement, Hip/or hip.mp. (107,123)
7. exp Hip Prosthesis/or exp Arthroplasty, Replacement, Hip/or hip replacement.mp. (31,655)
8. exp Hip Prosthesis/or total hip.mp. or exp Arthroplasty, Replacement, Hip/ (34,732)
9. hip arthroplasty.mp. (12,045)
10. total hip replacement.mp. or exp Arthroplasty, Replacement, Hip/ (20,706)
11. exp Arthroplasty, Replacement, Hip/or total hip arthroplasty.mp. (20,637)
12. exp Arthroplasty, Replacement, Hip/or exp Hip Prosthesis/or hip prosthes*.mp. (30,397)
13. 1-stage.mp. (1576)
14. 2-stage.mp. (2828)
15. one stage.mp. (8705)
16. two stage.mp. (15,977)
17. one-stage.mp. (8705)
18. two-stage.mp. (15,977)
19. single stage.mp. (4349)
20. single-stage.mp. (4349)
21. prosthesis exchange.mp. (15)
22. direct exchange.mp. (153)
23. direct-exchange.mp. (153)
24. Arthroplasty, Replacement, Hip/or revision arthroplasty.mp. (18,017)
25. exp Arthroplasty, Replacement, Hip/or staged revision.mp. (17,490)
26. reoperation.mp. or exp Reoperation/ (77,278)
27. reimplantation.mp. or exp Replantation/ (10,449)
28. 1 or 2 or 3 (1,606,087)
29. 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 (295,528)
30. 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 (129,343)
31. 28 and 29 and 30 (5795)

Appendix 16 Literature search terms for longitudinal studies of knee prosthetic joint infection as applied in MEDLINE on 31 August 2015 and described in *Surgical treatment of prosthetic joint infection: evidence from cohort studies*

1. exp Prosthesis-Related Infections/or prosthesis-related infection*.mp. (8340)
2. exp Infection/or infection.mp. (1,209,021)
3. wound infection.mp. or exp Wound Infection/ (44,719)
4. exp Surgical Wound Infection/or surgical infection.mp. (29,431)
5. exp Sepsis/or sepsis.mp. (129,398)
6. 1-stage.mp. (1578)
7. 2-stage.mp. (2833)
8. one stage.mp. (8710)
9. two stage.mp. (15,993)
10. one-stage.mp. (8710)
11. two-stage.mp. (15,993)
12. single stage.mp. (4354)
13. single-stage.mp. (4354)
14. exchange.mp. (231,326)
15. exp Prosthesis-Related Infections/or direct exchange.mp. (8465)
16. direct-exchange.mp. (153)
17. revision arthroplasty.mp. or exp Knee Prosthesis/ (9737)
18. staged revision.mp. (41)
19. reoperation.mp. or exp Reoperation/ (77,363)
20. reimplantation.mp. or exp Replantation/ (10,457)
21. reimplant*.mp. (6348)
22. 1 or 2 or 3 or 4 or 5 (1,235,959)
23. 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 (359,475)
24. arthroplasty.mp. or exp Arthroplasty, Replacement, Knee/or exp Arthroplasty, Replacement/or exp Arthroplasty/ (52,051)
25. exp Arthroplasty, Replacement/or Replacement.mp. or exp Arthroplasty, Replacement, Knee/ (204,563)
26. exp Knee/or exp Arthroplasty, Replacement, Knee/or knee.mp. (105,895)
27. exp Knee Joint/or exp Arthroplasty, Replacement, Knee/or exp Joint Prosthesis/or knee replacement.mp. or exp Knee Prosthesis/ (83,294)
28. exp Joint Prosthesis/or exp Knee Prosthesis/or exp Arthroplasty, Replacement, Knee/or Total knee.mp. or exp Knee Joint/ (83,497)
29. Knee arthroplasty.mp. or exp Arthroplasty, Replacement, Knee/ (16,575)
30. Knee prosthesis.mp. or exp Knee Prosthesis/ (9392)
31. Total knee replacement.mp. or exp Arthroplasty, Replacement, Knee/ (14,877)
32. exp Arthroplasty/or exp Knee Joint/or exp Arthroplasty, Replacement, Knee/or Total knee arthroplasty.mp. or exp Knee Prosthesis/ (83,930)
33. 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 (312,674)
34. 22 and 23 and 33 (7306)
35. limit 34 to humans (7197)

Appendix 17 Surgical treatment of prosthetic joint infection: the INFORM randomised controlled trial as summarised in *Surgical treatment of prosthetic joint infection: the INFORM randomised controlled trial*

Aims

Our aim was to determine whether or not there is a difference in patient-reported outcome measures 18 months after randomisation to single- or two-stage revision surgery for the treatment of hip prosthetic joint infection. Patients deemed to have infected hip replacements by their treating surgeons and multidisciplinary prosthetic joint infection teams were randomised to either single- or two-stage revision. Although the study was not powered to compare rates of reinfection or occurrence of new infection, adverse events including infection were monitored.

Methods

The INFORM trial was a multicentre, two-arm, parallel-group, participant and observer unblinded, randomised, superiority trial with 1 : 1 treatment allocation (ISRCTN10956306). Full details of the study design, methods and statistical analysis, along with the associated cost-effectiveness and qualitative studies are available in the published protocol.[97]

Trial oversight
The protocol was approved by the UK National Research Ethics Committee South West and the University of Gothenburg review board. The study was organised and co-ordinated by the Musculoskeletal Research Unit, University of Bristol, UK. An Independent Steering Committee and a Data Monitoring Committee oversaw the study.

Patients
A total of 140 patients were recruited from March 2015 to September 2018 from 15 secondary care orthopaedic units (11 in England, one in Wales and three in Sweden). Eligible patients were aged ≥ 18 years, had a clinical diagnosis of prosthetic hip joint infection and required treatment with single- or two-stage revision surgery.

Randomisation
Randomisation was conducted independently by the Bristol Randomised Trials Collaboration, a UK Clinical Research Collaboration-registered Clinical Trials Unit hosted by the University of Bristol. Randomisation was by secure remote third party, either via an internet-based application or by telephone. Randomisation was carried out as close to the time of surgery as possible, and no more than 12 weeks before surgery. It could not be carried out on the day of surgery due to the need to order equipment and for logistical planning in advance of surgery for these patients.

Allocation concealment was ensured by not releasing the treatment allocation until the patient had been recruited into the trial and all baseline measurements completed. Eligible participants who consented to the study were registered on the central trial database, were issued with a unique study identification number and had their baseline measures collected before the treatment allocation was generated, thereby ensuring that judgments about eligibility were made without knowledge of the next allocation.

Patients were randomly allocated in a 1 : 1 ratio to one of the intervention groups. Randomisation within blocks of randomly varying size (four or six) was stratified by hospital.

Interventions
Owing to the nature of the intervention and planning requirements, surgeons and patients were made aware of the assigned treatment shortly after the baseline assessment and randomisation had been carried out. Patients were assigned to either single- or two-stage revision surgery.

All other aspects of treatment, including antibiotics, analgesia, investigations, implants, static or articulating spacers, and surgical techniques and approach, were according to the treating surgeon's usual practice and in line with local policies and procedures. Usual clinical care continued throughout the study follow-up period.

Outcomes
Research assessments were carried out preoperatively and every 3 months until 18 months post randomisation. Data were collected from patient questionnaires and clinical performance tests and extracted from medical records.

The primary outcome measure was the WOMAC total score, measured at 18 months post randomisation. Eighteen months was chosen as the timing of the primary outcome as maximum recovery from all surgeries was expected to have been achieved and further health improvements were thought unlikely. The WOMAC index is a patient-reported outcome questionnaire divided into three subscales consisting of five pain, two stiffness and 17 physical function items. Response options are in a five-point Likert scale (0–4) format. Subscales of pain (score range 0–20), stiffness (score range 0–8) and function (score range 0–68) are summed to form a total score ranging from 0 (worst) to 96 (best). Raw scores were normalised to produces scores ranging from 0 (worst) to 100 (best).

As secondary outcomes, WOMAC scores were also measured every 3 months between 3 and 15 months post randomisation. Other patient-reported outcomes included the Brief Pain Inventory short form, Oxford Hip Score, Hip Dysfunction and Osteoarthritis Outcome and Hospital Anxiety and Depression Score. These were measured every 6 months between 6 and 18 months post randomisation. Patients were also invited to complete a 20-metre timed walk test after 18 months. Complications related to surgery, prosthetic joint infection or other reasons were identified from medical notes. Rehospitalisation and reoperation related to these complications were also identified. The presence of an infection between 15 and 18 months post randomisation was also considered as well as the serious adverse event.

Sample size
A sample size of 148 patients provided 80% power, with an attrition rate of 13%, to test that one surgical strategy was superior to the other strategy at 18 months post randomisation by 10 points on the WOMAC index, equivalent to a difference of 0.5 standard deviations. The significance level of this superiority hypothesis was set at 5% (two-sided). Although it is known that infection following total joint replacement reduces patient satisfaction and seriously impairs functional health and quality of life, there is no published research on the likely difference in patient-reported outcome between patients undergoing single-stage and those undergoing two-stage revision for prosthetic joint infection. The standard deviations observed prior to single-stage or two-stage revision surgery for total WOMAC score and subscores range between 18 and 25.[129,136] The attrition rate observed in a surgical trial involving total hip replacement recently conducted in the co-ordinating centre was 13%.[98]

Statistical analysis
The study was reported as per CONSORT guidelines and the analyses were performed according to the predefined analysis plan agreed with the Trial Steering Committee.

The main analysis was based on a two-level linear mixed-model regressing total WOMAC scores measured between 3 and 18 months post randomisation on the treatment effect and its interaction with a polynomial function of the time of assessment (first and second degrees). The model was also adjusted for baseline WOMAC and hospitals and had random effects at the patient level (measurement nested within participant). The difference in mean total WOMAC score at 18 months post randomisation between patients who received single-stage revision and those who received a two-stage revision (reference) was identified using linear combination of the treatment effect, the time of assessment and their interaction (contrast).

Although this modelling approach is robust to missing data when they are missing at random, multiple imputations with chained equations ($n = 33$) were conducted to include all randomised participants in the final analysis (imputed analysis). The imputation process was stratified by group.

To account for the fact that the WOMAC score is subject to a ceiling effect, the main analysis was replicated using a two-level tobit mixed model (Tobit analysis). Other sensitivity analyses included adjusting for sex, latest surgical treatment for the management of prosthetic joint infection prior to study participation and ASA grade at baseline, which were imbalanced between the groups (adjusted analysis, adjusted and imputed analysis). All of these analyses were based on the intention-to-treat principle.

A sensitivity analysis was performed on all randomised participants undergoing operations in centres in which the single-stage or two-stage procedure was not systematically performed with a CUMARS.

The secondary outcomes were modelled using a similar strategy and appropriate generalised linear mixed model depending on their distribution. Dichotomous outcomes such as complication, rehospitalisation or reoperation status with no repeated measurements were analysed with a generalised linear model, such as the log-binomial regression.

Results

A CONSORT flow diagram is shown in *Figure 15*. Of 186 patients eligible for inclusion in the trial, 65 were randomised to single-stage revision and 75 were randomised to two-stage revision. The baseline characteristics of participants in the randomised groups, shown in *Table 13*, were balanced between the groups, except that patients in the single-stage group were more likely to be male, to have ASA grade one or two and to have received previous non-surgical management for their infection. The groups were similar in the number and type of organisms cultured, rates of culture-negative infection and presence of a sinus tract. A total of 126 (90%) patients had the primary total WOMAC score outcome at 18 months post randomisation, and 133 (95%) patients had at least one postoperative total WOMAC score and were included in the main analysis.

In the single-stage group, 55 (84.6%) patients received their assigned intervention, eight received a two-stage procedure and one did not receive a revision. Four patients withdrew during follow-up and two died. In the two-stage group, 68 (90.7%) patients received their assigned intervention, five received an alternative revision procedure and one did not receive a revision. Three patients withdrew during follow-up and five died. The median time between stages in the two-stage group was 3.7 months (IQR 2.6–6.1 months).

Primary outcome

There was no evidence of a difference in the mean total WOMAC score at 18 months post randomisation between single- and two-stage management of hip prosthetic joint infection (mean difference favouring two stage 0.13, 95% CI –8.20 to 8.46; $p = 0.98$).

TABLE 13 Participant baseline characteristics

Characteristic	Category	Single-stage		Two-stage	
		n	%	*n*	%
Age at inclusion (years)	Mean (SD)	65	70.0 (9)	75	72 (10)
BMI (kg/m²)	Mean (SD)	65	29.0 (7)	75	29 (5)
Sex	Female	20	30.8	31	41.3
	Male	45	69.2	44	58.7
Ethnicity	Non-white	1	1.5	2	2.7
	White	64	98.5	73	97.3
ASA grade	1	2	3.1	1	1.3
	2	28	43.1	29	38.7
	3	26	40.0	38	50.7
	4	2	3.1	0	0.0
	Missing	7	10.8	7	9.3
Work status	Receiving sick pay	6	9.2	3	4.0
	Retired	44	67.7	58	77.3
	Unemployed	2	3.1	3	4.0
	Working full time	9	13.9	9	12.0
	Working part time	4	6.2	2	2.7
Number of comorbidities	None	7	10.8	10	13.3
	One	18	27.7	18	24.0
	Three	9	13.9	10	13.3
	Two	16	24.6	21	28.0
	Four or more	15	23.1	16	21.3
Home status	Alone	18	27.7	24	32.0
	With husband/wife/partner	47	72.3	45	60.0
	With somebody else	0	0.0	6	8.0
Marital status	Divorced/separated	6	9.2	8	10.7
	Married/partner	49	75.4	46	61.3
	Single	7	10.8	5	6.7
	Widowed	3	4.6	16	21.3

SD, standard deviation.

Secondary outcomes

At 3 months post randomisation, participants in the single-stage group had a better total WOMAC score (mean difference favouring single stage 11.53, 95% CI 3.89 to 19.17; *p* = 0.003). From 6 months post randomisation onwards, no evidence of a difference was found between the two surgical procedures. Similar findings were found for all patient outcomes.

There was a higher rate of complications of surgery in patients receiving a two-stage revision than in those receiving a single-stage revision (57.3% vs. 41.5%; $p = 0.04$) and this difference was marked for intraoperative events (26.7% vs. 7.7%; $p = 0.01$), predominantly calcar cracks and femoral shaft fractures (18 vs. 3). There was no evidence of a difference between the groups in length of stay; other complications; rehospitalisation or reoperation due to prosthetic joint infection, the surgery or another cause; serious adverse events; or deaths (5 vs. 2). Rates of serious adverse events, rehospitalisations, reoperations and deaths were similar between the groups. At 15–18 months post randomisation, 9 out of 59 (15%) patients who received single-stage revision had signs of infection in the operated hip, compared with 8 out of 67 (12%) people who received two-stage revision ($p = 0.59$).

Rates of serious adverse events and deaths were similar in the groups.

Conclusion

The INFORM trial demonstrated that single- and two-stage revisions are equally efficacious for the treatment of prosthetic joint infection. However, an early functional benefit was seen in the single-stage group and, given that patients stated a strong preference for a quick return to normal activity, this should be considered when selecting the intervention. Single-stage surgery accounted for 30% of revision procedures for the treatment of prosthetic joint infection in 2014, so there is scope for increased utilisation.

Limitation

The INFORM sample size precluded study of reinfection outcome.

Appendix 18 Surgical treatment of prosthetic joint infection: the INFORM randomised controlled trial cost-effectiveness analysis as described in *Surgical treatment of prosthetic joint infection: the INFORM randomised controlled trial health economic analysis*

Background

In the INFORM RCT we incorporated an economic evaluation to determine the cost-effectiveness of a single-stage compared with a two-stage revision strategy in patients with hip prosthetic joint infection.

Methods

Resource use measurement and valuation

Data on health service, PSS and participant resource use relating to the revision surgery for hip prosthetic joint infection and any subsequent treatments were collected over 18 months from randomisation from trial case report forms and patient-completed questionnaires.

Study research nurses from treating hospitals recorded resource use information on case report forms for the revision surgeries, postoperative inpatient stays and outpatient visits relating to hip infection. This included surgery time, types and brands of implants used, local and systemic antibiotics, time spent and resources used on postoperative wards. Case report forms were completed at 3, 6, 9, 12, 15 and 18 months post randomisation.

The self-reported resource use questionnaire was posted to participants at the 6-, 12- and 18-month follow-ups and was used to collect the following information concerning their prosthetic joint infection: community-based health-care use (e.g. general practitioner appointments and district nurse attendances), prescribed medications and emergency department attendances; social service provision received; personal expenses, including travel and home changes; informal care; and time off work and usual activities.

Resources used and the unit costs (GBP in 2018/19 prices) used to value them are shown in *Table 14*.

Outcome measurement

The primary outcome of the economic analysis was the QALY as recommended by NICE.[146] The baseline EQ-5D-5L was completed at a clinic or home visit. At 3 months the questionnaire was completed over the telephone, and at 6, 12 and 18 months postal questionnaires were completed.

Utility values were estimated from the EQ-5D-5L using the validated mapping function to the existing EQ-5D-3L societal UK utility tariffs.[104] QALYs were calculated by linear interpolation using the area-under-the-curve approach, taking into account any deaths that occurred during the study period by allocating those who died a zero utility in the time period following their death.[105]

TABLE 14 Resources collected and their valuation (2018/19 prices excluding VAT)

Resource	Unit cost (£)	Source of cost
Theatre time	29.91 per minute[a]	Finance department of treating hospital
Implants	Varies[b]	National Joint Registry[8]
HDU/ICU	42.12 per hour	Finance department of treating hospital
Ward	12.62 per hour	Finance department of treating hospital
Radiological tests	Varies	*NHS Reference Costs 2018 to 2019*[101]
Biochemistry tests	1.11	*NHS Reference Costs 2018 to 2019*[101]
Haematology tests	2.51	*NHS Reference Costs 2018 to 2019*[101]
Microbiology tests	7.59	*NHS Reference Costs 2018 to 2019*[101]
Overheads	9.60 per hour on ward	Finance department of treating hospital
Subsequent inpatient admissions	Varies[c]	*NHS Reference Costs 2018 to 2019*[101]
Outpatient appointments	Varies[d]	*NHS Reference Costs 2018 to 2019*[101]
Outpatient procedures	Varies	*NHS Reference Costs 2018 to 2019*[101]
Accident and emergency attendances (no admission)	132.88	*NHS Reference Costs 2018 to 2019*[101]
General practitioner (surgery)	39.23	*Unit Costs of Health and Social Care 2019*[102]
General practitioner (home)	124.51	*Unit Costs of Health and Social Care 2013*[137]
General practitioner (telephone)	8.00	*Unit Costs of Health and Social Care 2019*[102]
Nurse (surgery)	10.85	*Unit Costs of Health and Social Care 2019*[102]
Nurse (home)	21.98	*Unit Costs of Health and Social Care 2019*[102]
Nurse (telephone)	5.53	*Unit Costs of Health and Social Care 2019*[102]
GP receptionist	7.80	*Unit Costs of Health and Social Care 2019*[102]
Phlebotomist	3.51[e]	*Unit Costs of Health and Social Care 2018*[138]
District nurse	40.16[e]	*Unit Costs of Health and Social Care 2015*[139]
Occupational therapist	34.00	*Unit Costs of Health and Social Care 2019*[102]
Community physiotherapist	54.00	*Unit Costs of Health and Social Care 2019*[102]
NHS 111 service	13.39 per call	Turner *et al.*[140]
Other community care	Varies	*Unit Costs of Health and Social Care 2019*,[102] *NHS Reference Costs 2018 to 2019*[101]
Medications	Varies[f]	*British National Formulary*[141]
Prescription charges	9.15 per item	NHS[142]
Residential home stay	Aged 18–64 years: £135 per day Aged ≥ 65 years: £146 per day	*Unit Costs of Health and Social Care 2019*[102]
Home care worker	28.29 per hour[g]	*Unit Costs of Health and Social Care 2019*[102]
Home changes and equipment	Varies	NRS Healthcare,[143] *Unit Costs of Health and Social Care 2019*[102]

TABLE 14 Resources collected and their valuation (2018/19 prices excluding VAT) (*continued*)

Resource	Unit cost (£)	Source of cost
Wage rate	14.67 per hour[h]	ONS Annual Survey of Hours and Earnings[144]
Travel cost per journey	Varies	The patient's reported mode of transport to each health-care facility and the fare/miles[i] reported were used to create a mean unit cost for travel to each health facility

GP, general practitioner; HDU, high-dependency unit; ICU, intensive care unit; NRS, Nottingham Rehabilitation Services; ONS, Office for National Statistics; VAT, value-added tax.
a Includes surgical staff, anaethetists, anaesthetics, blood products, consumables and theatre overheads.
b The NJR provided a mean cost of each different type of implant. It created this mean cost from the costs supplied by individual hospitals. Where the NJR was unable to supply a cost, the mean cost of the component, based on the type of surgery and the type of cup and stem fixed, was used.
c Includes medical staff, pharmacy services, clinical photography, therapies, drugs, major trauma, overheads – inpatient specialty, overheads – specialty, and overheads – other. The elective inpatient cost related to the relevant HRG was used.
d A consultant-led or non-consultant-led unit cost relating to the relevant service code (i.e. specialty) was used.
e Costs inflated to 2019–20 values using the NHS Cost Inflation Index.
f Costs calculated on stated dosage and frequency; if this was missing, usual dose was used.
g Cost based on weighted average of weekday and weekend face-to-face costs of independent sector home care provided for social services.
h Based on median hourly earnings for public sector given total weekly paid hours of 37.
i Mileage was costed using NHS Terms and Conditions of Service Handbook.[145]

Missing data

To account for missing data, multiple imputation by chained equations using predictive mean matching was used. Simple imputation methods assuming zero resource use within a returned participant questionnaire for item non-response, and using mean imputation where a participant had indicated use of a resource with no further details, were used prior to multiple imputation for the imputation to converge. Missing values for baseline utility were also imputed using the mean baseline utility value,[106] prior to multiple imputation. The covariates in the imputation model were baseline utility, trial group, age, sex, ethnicity, education status, work status, centre, ASA grade of first revision surgery, and the latest surgical treatment for the management of prosthetic joint infection prior to study participation. Rubin's rules were used to combine the 68 individual imputations, and a randomisation seed was used to enable reproducible imputations.[99]

Analysis

Analyses were conducted using an intention-to-treat approach, analysing the groups as they were randomised. Stata version 15.1 (StataCorp LP, College Station, TX, USA) was used for statistical analysis. Any costs occurring between 12 and 18 months post randomisation were discounted at a rate of 3.5% per year as recommended by NICE.[146]

Items were grouped into resource use categories and summed for each participant. Unadjusted costs from a treating hospital perspective were estimated by group for three time periods (0–6 months, 6 months to 1 year and 1 year to 18 months). The adjusted mean costs and QALYs by trial group and the differences in adjusted mean costs and QALYs (with 95% CIs) between the trial groups were estimated using the seemingly unrelated regressions method, which accounts for the correlation between costs and QALYs.[107] Costs and QALYs were adjusted for study centre. QALYs were additionally adjusted for baseline utility.

The iNMB was calculated parametrically using seemingly unrelated regression outputs, which represent the value of the intervention in monetary terms where a willingness-to-pay threshold for a unit of benefit is known. The NICE willingness-to-pay thresholds of £20,000 and £30,000 per QALY were used.[146] When the iNMB is positive, the single-stage revision surgery can be identified as cost-effective relative to two-stage revision surgery.

Allowance for uncertainty

Sample uncertainty in the cost-effectiveness estimates was explored using CEACs.[147] These were calculated from the net monetary benefit values at each threshold of willingness-to-pay per QALY (£0 to £100,000 in £1000 increments). The CEAC shows the probability that the single-stage is the cost-effective option compared with two-stage at different thresholds of willingness to pay per QALY.

Deterministic one-way sensitivity analyses were undertaken to examine the impact of changes in key parameters on the iNMB by modifying the value of one parameter at a time within a plausible range:

- Including Swedish participants. These participants were excluded from the primary analysis because of differences in data collection and health-care jurisdiction.
- Applying HRG costs to all intervention and subsequent surgeries as an alternative to the microcosting approach applied in the primary analysis to address the generalisability of health-care costs.
- Using alternative discount rates of 2% and 5%.
- Conducting an analysis adjusting for sex, latest surgical treatment for the management of prosthetic joint infection prior to study participation and ASA grade at baseline, which were imbalanced between the groups.
- Conducting a complete-case analysis from a treating hospital perspective.
- Conducting two analyses from a treating hospital perspective with two different specifications of the multiple imputation model to examine the impact of model structure on the results: one in which the multiple imputation model was conducted by group and the other in which this was not the case.

Results

The differences in the collection of data for UK and Swedish participants, and the differences in the health-care jurisdictions of the two countries, meant that the primary economic analysis was conducted on 128 UK participants (91% of the total sample). Resource use and cost data from the treating hospitals were available for 114 UK participants (89%). With the inclusion of patient questionnaire information, the proportion of participants with complete data from an NHS/PSS perspective was 41%. Thus, multiple imputation was used to create the data set comprising all 128 UK participants on whom the analyses of costs, QALYs and cost-effectiveness were conducted. *Table 15* shows the proportion of missing data for each variable in the multiple imputation model.

Total theatre time was approximately 76 minutes longer for those randomised to two-stage revision surgery, and these patients spent a longer time in high-dependency or intensive therapy units and recovery and had a longer hospital stay (*Table 16*). They also had a greater number of subsequent inpatient stays and emergency department attendances. Those randomised to a single-stage procedure had a greater number of primary care practice nurse visits, whereas those randomised to a two-stage procedure had a greater number of district nurse home visits, stays in residential homes and home care worker visits. Participants randomised to two-stage revision took a greater number of hours of paid leave and lost a greater number of hours from usual activities, whereas those randomised to a single-stage revision lost more working hours in terms of permanently giving up work and permanent reduction in hours worked.

The EQ-5D-5L utility values in *Table 17* illustrate the different pathways of the two procedures, with those randomised to the single-stage procedure seeing a gradual improvement in their utility values from 3 months onwards, whereas for those randomised to the two-stage procedure the improvement only began at 6 months.

As shown in *Table 18*, the mean costs of surgical admissions were higher in the first year of follow-up in the single-stage group; however, in the last 6 months of the trial these costs were similar in both trial groups, with these being slightly more costly in the single-stage group (£1593 vs. £1489). The costs of follow-up outpatient visits and non-surgical admissions were similar in the first year, with these being more expensive in the two-stage revision surgery group in the final 6 months (£702 vs. £484).

TABLE 15 The percentage of missing data for each variable following simple mean and zero imputation for the variables included in the multiple imputation model

Variable	Components	Missing (n) (N = 128)	Missing (%)
Surgery total costs	Surgery antibiotics, surgery anaesthetics, theatre time	4	3
Implant total costs	Implant costs, cement costs	5	4
Ward total costs	Ward costs and overhead costs	5	4
HDU/ICU costs	HDU and ICU costs	6	5
Hospital antibiotic costs	Hospital-prescribed antibiotics	5	4
Surgery follow-up admissions	Inpatient stays for follow-up surgery (not single- or two-stage surgeries)	3	2
Hospital follow-up costs (treating hospital)	Outpatient appointments, outpatient procedures, inpatient stays	9	7
Non-treating-hospital follow-up admissions	Inpatient stays in hospitals other than where the revision surgery took place	36	28
Non-treating hospital outpatient visits	Outpatient visits to hospitals other than where the revision surgery took place	36	28
A&E total costs (6 months)	A&E visits	24	19
A&E total costs (12 months)	A&E visits	23	18
A&E total costs (18 months)	A&E visits	25	20
GP and community-based health care (6 months)	GP practice, GP home visits, GP telephone calls, GP practice nurse visits, GP practice nurse telephone calls, phlebotomist visits, GP receptionist visits, district nurse home visits, occupational therapist home visits, physiotherapist home visits, physiotherapist practice visits, NHS Direct telephone calls, other community care	25	20
GP total (12 months)	Components as for GP and community-based health care	24	19
GP total (18 months)	Components as for GP and community-based health care	23	18
Medications total costs (6 months)	GP-prescribed medication costs	42	33
Medications total costs (6 months)	GP-prescribed medication costs	44	34
Medications total costs (12 months)	GP-prescribed medication costs	39	30
Residential and home care costs (6 months)	Residential/nursing home costs, home care worker costs, home changes and equipment	33	26
Residential and home care costs (12 months)	Residential/nursing home costs, home care worker costs, home changes and equipment	33	26
Residential and home care costs (18 months)	Residential/nursing home costs, home care worker costs, home changes and equipment	35	27
EQ-5D utility (3 months)	EQ-5D utility	16	13
EQ-5D utility (6 months)	EQ-5D utility	27	21
EQ-5D utility (12 months)	EQ-5D utility	23	18
EQ-5D utility (18 months)	EQ-5D utility	16	13
Prescription and one-off expenses (6 months)	Prescribed medications, major one-off expenses	29	23

TABLE 15 The percentage of missing data for each variable following simple mean and zero imputation for the variables included in the multiple imputation model (*continued*)

Variable	Components	Missing (*n*) (*N* = 128)	Missing (%)
Prescription and one-off expenses (12 months)	Prescribed medications, major one-off expenses	30	23
Prescription and one-off expenses (18 months)	Prescribed medications, major one-off expenses	32	25
Lost work (6 months)	Lost work hours, paid leave, unpaid leave	7	5
Lost work (12 months)	Lost work hours, paid leave, unpaid leave	3	2
Lost work (18 months)	Lost work hours, paid leave, unpaid leave	6	5
Additional support (6 months)	Additional support hours required	28	22
Additional support (12 months)	Additional support hours required	26	20
Additional support (18 months)	Additional support hours required	26	20
Patient home care costs (6 months)	Home care changes and home care costs: patient contributions	32	25
Patient home care costs (12 months)	Home care changes and home care costs: patient contributions	33	26
Patient home care costs (18 months)	Home care changes and home care costs: patient contributions	35	27
Usual activities (6 months)	Usual activity hours lost	25	20
Usual activities (12 months)	Usual activity hours lost	23	18
Usual activities (18 months)	Usual activity hours lost	25	20
Hospital travel	Costs of travel to treating hospital	21	16
Hospital travel	Costs of travel to non-treating hospital	36	28
GP and community-based travel (6 months)	Travel costs to GP and community-based services	28	22
GP and community-based travel (12 months)	Travel costs to GP and community-based services	27	21
GP and community-based travel (18 months)	Travel costs to GP and community-based services	29	23

A&E, accident and emergency; EQ-5D, EuroQol-5 Dimensions; GP, general practitioner; HDU, high-dependency unit; ICU, intensive care unit.

TABLE 16 Mean (95% CI) resource use by category and randomised allocation

Resource use category (unit of measurement)	Single-stage revision surgery		Two-stage revision surgery	
	n	Mean resource use (95% CI)	*n*	Mean resource use (95% CI)
Theatre time (minutes)[a]	59	333.85 (294.29 to 373.41)	65	409.62 (364.81 to 454.43)
Recovery ward (minutes)[b]	56	487.16 (−52.01 to 1026.33)	61	716.75 (454.90 to 978.62)
Total high-dependency/intensive therapy units (hours)	58	25.43 (12.22 to 38.63)	64	30.06 (16.15 to 43.97)
Implant costs (£)[c]	59	1948.41 (1644.54 to 2252.28)	64	2391.68 (2033.27 to 2750.09)
Total preoperative stay (hours)	59	17.42 (8.44 to 26.41)	65	15.21 (11.14 to 19.27)
Total postoperative stay (days)	59	20.83 (16.09 to 25.57)	64	27.11 (20.90 to 33.33)

TABLE 16 Mean (95% CI) resource use by category and randomised allocation (*continued*)

Resource use category (unit of measurement)	Single-stage revision surgery		Two-stage revision surgery	
	n	Mean resource use (95% CI)	n	Mean resource use (95% CI)
Total inpatient tests (radiology, microbiology, biochemisty, haematology) (n)	59	44.73 (33.42 to 56.03)	65	49.05 (37.86 to 60.24)
Subsequent non-surgical inpatient stays (number of stays)	56	0.20 (0.05 to 0.34)	63	0.32 (0.18 to 0.50)
Subsequent outpatient visits (number of visits)	56	4.79 (4.16 to 5.41)	63	5.40 (4.65 to 6.14)
Outpatient procedure-only visits (number of procedures)	56	0.41 (0.13 to 0.69)	63	0.24 (0.10 to 0.38)
Non-treating-hospital inpatient stays (number of stays)	41	0.10 (−0.02 to 0.22)	51	0.35 (0.14 to 0.57)
Non-treating-hospital outpatient visits (number of visits)	41	0.54 (0.08 to 0.99)	51	0.25 (0.05 to 0.46)
Emergency department (number of non-admission visits)	41	0.12 (−0.04 to 0.28)	51	0.33 (0.12 to 0.55)
Primary care clinician: surgery (number of visits)[d]	41	2.30 (0.38 to 4.22)	51	1.94 (0.85 to 3.04)
Primary care clinician: home (number of visits)[d]	41	0.17 (−0.73 to 0.42)	51	0.32 (0.01 to 0.63)
Telephone calls with primary care clinician (number of telephone calls)[d]	41	0.61 (0.18 to 1.04)	51	1.51 (0.38 to 2.63)
Primary care practice nurse visits (number of visits)[d]	41	3.82 (1.14 to 6.51)	51	1.77 (0.87 to 2.68)
Telephone calls with primary care practice nurse (number of telephone calls)[d]	41	0.14 (−0.04 to 0.32)	51	0.36 (0.11 to 0.61)
District nurse (number of home visits)[d]	41	2.23 (−0.37 to 4.84)	51	8.93 (2.38 to 15.49)
Other community-based health service contacts (number of contacts)[d]	41	15.53 (5.57 to 25.49)	51	16.64 (3.35 to 30.92)
Antibiotic medications (number of medications prescribed by hospital)[b]	59	6.00 (4.98 to 7.02)	65	6.12 (5.29 to 6.95)
Medications (number of medications prescribed by primary care clinician)	39	1.59 (0.86 to 2.32)	46	2.72 (1.66 to 3.78)
Residential home/nursing home (number of nights)	41	2.61 (−1.16 to 6.38)	51	11.96 (−0.75 to 24.68)
Home changes/equipment: NHS/PSS-provided (number of home changes/equipment)	39	2.31 (1.23 to 3.38)	46	2.50 (1.75 to 3.25)
Home changes/equipment: privately purchased (number of home changes/equipment)	39	0.56 (0.07 to 1.06)	46	1.52 (0.67 to 2.37)
Home care worker (number of visits)	38	19.58 (−2.71 to 41.87)	46	51.22 (4.54 to 97.90)
Prescription charges (number of charges)	39	0.05 (−0.05 to 0.16)	46	0.30 (−0.09 to 0.70)
One-off expenses (number of items)	39	0.23 (0.09 to 0.37)	46	0.33 (0.12 to 0.53)
Working hours lost (number of hours)[e]	53	101.89 (−17.11 to 220.89)	66	80.70 (−1.30 to 162.69)
Hours of paid leave (number of hours)	53	17.97 (−5.64 to 41.59)	66	44.31 (−14.87 to 103.51)

TABLE 16 Mean (95% CI) resource use by category and randomised allocation (*continued*)

Resource use category (unit of measurement)	Single-stage revision surgery		Two-stage revision surgery	
	n	Mean resource use (95% CI)	*n*	Mean resource use (95% CI)
Hours of unpaid leave (number of hours)	53	23.63 (–5.07 to 52.33)	66	10.45 (–4.88 to 25.79)
Usual activity hours lost (number of hours)[f]	40	274.96 (154.36 to 395.55)	51	625.86 (337.78 to 913.95)
Additional support/care hours (number of hours)[f]	38	274.08 (153.18 to 394.98)	48	610.56 (400.33 to 820.79)

a Theatre time was calculated from time patient entered theatre to time patient left theatre.
b These resources are presented for information only; they were not costed in the analysis.
c Includes costs of cement.
d These figures accounted for missing frequency data using mean imputation.
e Inclusive of hours lost due to permanent stoppages and permanent reduction in hours of work. Excludes any paid and unpaid leave.
f Based on average number of hours per week in each month.

TABLE 17 Mean (95% CI) unadjusted EQ-5D-5L utility value by time point and randomised allocation[a]

EQ-5D utility	Single-stage revision surgery		Two-stage revision surgery	
	n	Mean utility (95% CI)	*n*	Mean utility (95% CI)
EQ-5D utility (baseline)	60	0.32 (0.23 to 0.41)	67	0.28 (0.20 to 0.36)
EQ-5D utility (3 months)	50	0.51 (0.41 to 0.61)	62	0.33 (0.23 to 0.42)
EQ-5D utility (6 months)	45	0.54 (0.44 to 0.64)	56	0.46 (0.37 to 0.55)
EQ-5D utility (12 months)	49	0.54 (0.44 to 0.64)	56	0.50 (0.42 to 0.59)
EQ-5D utility (18 months)	52	0.60 (0.50 to 0.70)	60	0.60 (0.52 to 0.68)

EQ-5D, EuroQol-5 Dimensions.
a With the exception of baseline utility (missing values imputed using mean baseline utility scores), complete-case values are given.

TABLE 18 Mean unadjusted treating hospital surgical admissions and follow-up by time period and randomised allocation[a]

Surgical admissions and follow-up outpatient visits	Single-stage revision surgery		Two-stage revision surgery	
	n	Mean cost (£) (95% CI)	*n*	Mean cost (£) (95% CI)
Surgical admissions (0–6 months)	58	21,287 (18,250 to 24,323)	62	25,674 (21,696 to 29,652)
Follow-up outpatient visits and admissions (0–6 months)	56	894 (123 to 1664)	63	820 (427 to 1213)
Surgical admissions (6–12 months)	58	2039 (613 to 3466)	62	3660 (1688 to 5632)
Follow-up outpatient visits and admissions (6–12 months)	56	437 (72 to 802)	63	444 (181 to 707)
Surgical admissions (12–18 months)	58	1593 (–426 to 3612)	62	1489 (–76 to 3055)
Follow-up outpatient visits and admissions (12–18 months)	56	484 (453 to 516)	63	702 (443 to 962)

a Complete-case values are given.

The total adjusted mean costs from the NHS/PSS perspective in the single-stage group (£36,256) were lower than in the two-stage group (£46,312), a cost difference of –£10,055 (95% CI –£19,568 to –£542) (*Table 19*). The cost difference reduced slightly from the societal perspective (–£9450, 95% CI –£22,855 to £3956).

Participants in the single-stage group also had a greater number of adjusted mean QALYs (0.75) than those in the two-stage group (0.69), a difference of 0.06 (95% CI–0.07 to 0.18) (*Table 20*).

From the NHS/PSS perspective, the iNMB of single-stage compared with two-stage was £11,167 (95% CI £638 to £21,696) at the willingness-to-pay threshold of £20,000 per QALY and £11,723 (95% CI £507 to £22,938) at the willingness-to-pay threshold of £30,000 per QALY. The iNMB was slightly smaller from the societal perspective, at £10,589 (95% CI –£3855 to £25,033) at the threshold of £20,000 per QALY.

Figure 18 shows the CEACs from both perspectives and indicates that, at a willingness-to-pay threshold of £20,000 per QALY, the probability that a single-stage procedure is the cost-effective treatment compared with a two-stage procedure is 98% from the NHS/PSS perspective and 92% from the societal perspective.

The sensitivity analyses (see *Table 20*) conducted from the NHS/PSS perspective did not show any reduction in the probability that the single-stage procedure was cost-effective. Including participants from Sweden, using HRG costs and a 5% discount rate led to a slight increase in the difference between mean costs, whereas the adjusted analysis led to a slight decrease in the difference between the groups. Using HRG costs led to substantial reductions in costs for both groups. The difference in QALYs remained the same, apart from when patients from Sweden were included, which resulted in an increase in the difference from 0.06 to 0.07. From the treating hospital perspective, the complete-case analysis showed an increase in the probability of the single stage being cost-effective to 99.7%. There was a larger difference in cost between the two groups compared with both multiple imputation analyses from this perspective. The results of the two multiple imputation analyses were similar, and the probability that the single-stage treatment was cost-effective reduced to just under 95%.

Discussion

From all perspectives, participants randomised to a single-stage procedure had both lower costs and more QALYs than those randomised to a two-stage procedure. A difference in QALYs of 0.06 equates to an extra 33 days in best imaginable health during the 18 months in favour of participants who had a single-stage procedure.

The two hospital stays involved with a two-stage procedure led to the higher cost in this arm. The EQ-5D-5L scores illustrate that while the participants in this group were awaiting their second-stage operation they had a poorer quality of life, which was reflected in the overall QALY score. The greater use of district nurse home visits and home care worker visits indicates that these participants were also less able to self-care and leave their home during this time.

The analysis has limitations, mainly relating to the resource use data obtained from the self-completed questionnaire. A complete case could be conducted only from a treating hospital perspective, and indicated higher QALY values in both groups, indicating that those who did not complete all of the questionnaires were likely to have poorer quality of life than those who did. Multiple imputation was therefore needed because only 41% of patients had complete resource use data from an NHS/PSS perspective and only 36% had these from a societal perspective. It was not possible to run multiple imputation by group from either the NHS/PSS or the societal perspective. Maximising the number of complete data by using data at each time point in the model had to be traded against the sample size.

TABLE 19 Cost–consequences results[a]

Treatment	n	Adjusted costs[a] (£), mean (95% CI)	Adjusted QALYs,[a] mean (95% CI)	Incremental costs (95% CI)	Incremental QALYs (95% CI)	iNMB (£) at £20,000/QALY (95% CI)	iNMB (£) at £30,000/QALY (95% CI)
NHS and PSS perspective							
Single stage	60	36,256 (29,344 to 43,169)	0.75 (0.65 to 0.84)				
Two stage	68	46,312 (39,876 to 52,747)	0.69 (0.61 to 0.77)	–10,055 (–19,568 to –542)	0.06 (–0.07 to 0.18)	11,167 (638 to 21,696)	11,723 (507 to 22,938)
Societal perspective							
Single stage	60	51,420 (41,551 to 61,288)	0.75 (0.65 to 0.84)				
Two stage	68	60,870 (51,864 to 69,878)	0.69 (0.61 to 0.77)	–9450 (–22,855 to 3956)	0.06 (–0.07 to 0.18)	10,589 (–3855 to 25,033)	11,158 (–3936 to 26,252)

a All variables are adjusted for hospital site. Additionally, QALYs are adjusted for baseline utility score.

TABLE 20 Results of the sensitivity analysis (from NHS and PSS perspective unless specified otherwise)

Treatment	n	Adjusted mean costs[a] (£), mean (95% CI)	Adjusted QALYs,[a] mean (95% CI)	Incremental costs (95% CI)	Incremental QALYs (95% CI)	iNMB (£) at £20,000/QALY (95% CI)	iNMB (£) at £30,000/QALY (95% CI)	Probabiity cost-effective at £20,000 per QALY
Inclusion of Swedish patients								
Single stage	65	34,758 (28,413 to 41,102)	0.78 (0.69 to 0.86)					
Two stage	75	44,896 (39,118 to 50,675)	0.71 (0.63 to 0.79)	−10,138 (−18,738 to −1539)	0.07 (−0.05 to 0.19)	11,515 (1936 to 21,093)	12,203 (1955 to 22,452)	0.99
Using HRG costs rather than microcosting for the surgical admissions								
Single stage	60	26,072 (21,260 to 30,883)	0.75 (0.65 to 0.84)					
Two stage	68	37,270 (32,851 to 41,690)	0.69 (0.61 to 0.77)	−11,199 (−17,779 to −4619)	0.06 (−0.07 to 0.18)	12,304 (4707 to 19,902)	12,857 (4510 to 21,205)	0.99
2% discount rate								
Single stage	60	35,953 (29,074 to 42,833)	0.75 (0.66 to 0.85)					
Two stage	68	45,760 (39,277 to 52,242)	0.69 (0.61 to 0.77)	−9806 (−19,234 to −379)	0.06 (−0.06 to 0.19)	11,084 (543 to 21,625)	11,723 (446 to 23,001)	0.98
5% discount rate								
Single stage	60	35,945 (29,036 to 42,854)	0.74 (0.65 to 0.84)					
Two stage	68	46,106 (39,569 to 52,643)	0.69 (0.60 to 0.77)	−10,161 (−19,646 to 677)	0.06 (−0.07 to 0.18)	11,313 (740 to 21,886)	11,889 (597 to 23,181)	0.98
Adjusted analysis (adjusting for sex, latest surgical treatment for the management of PJI prior to study participation and ASA grade at baseline)								
Single stage	60	36,586 (29,747 to 43,426)						
Two stage	68	46,021 (39,684 to 52,357)	0.69 (0.60 to 0.77)	−9434 (−18,929 to 61)	0.06 (−0.06 to 0.19)	10,694 (215 to 21,173)	11,324 (173 to 22,474)	0.98

TABLE 20 Results of the sensitivity analysis (from NHS and PSS perspective unless specified otherwise) (*continued*)

Treatment	n	Adjusted mean costs[a] (£), mean (95% CI)	Adjusted QALYs,[a] mean (95% CI)	Incremental costs (95% CI)	Incremental QALYs (95% CI)	iNMB (£) at £20,000/QALY (95% CI)	iNMB (£) at £30,000/QALY (95% CI)	Probabiity cost-effective at £20,000 per QALY
Treating hospital perspective: complete case								
Single stage	38	27,316 (22,548 to 32,084)	0.78 (0.68 to 0.88)					
Two stage	44	36,699 (32,282 to 41,116)	0.72 (0.63 to 0.81)	−9383 (−16,022 to −2744)	0.06 (−0.08 to 0.20)	10,584 (2961 to 18,207)	11,184 (2761 to 19,608)	1.00
Treating hospital perspective: MI (by group)								
Single stage	60	29,855 (25,011 to 34,700)	0.77 (0.67 to 0.88)					
Two stage	68	34,894 (30,321 to 39,467)	0.71 (0.61 to 0.80)	−5038 (−11,748 to 1671)	0.07 (−0.07 to 0.20)	6371 (−1312 to 14,053)	7037 (−1420 to 15,494)	0.95
Treating hospital perspective: MI (not by group)								
Single stage	60	29,728 (24,875 to 34,581)	0.78 (0.66 to 0.89)					
Two stage	68	34,972 (30,421 to 39,523)	0.73 (0.64 to 0.82)	−5243 (−11,932 to 1445)	0.05 (−0.10 to 0.21)	6263 (−1392 to 13,918)	6773 (−1746 to 15,292)	0.95

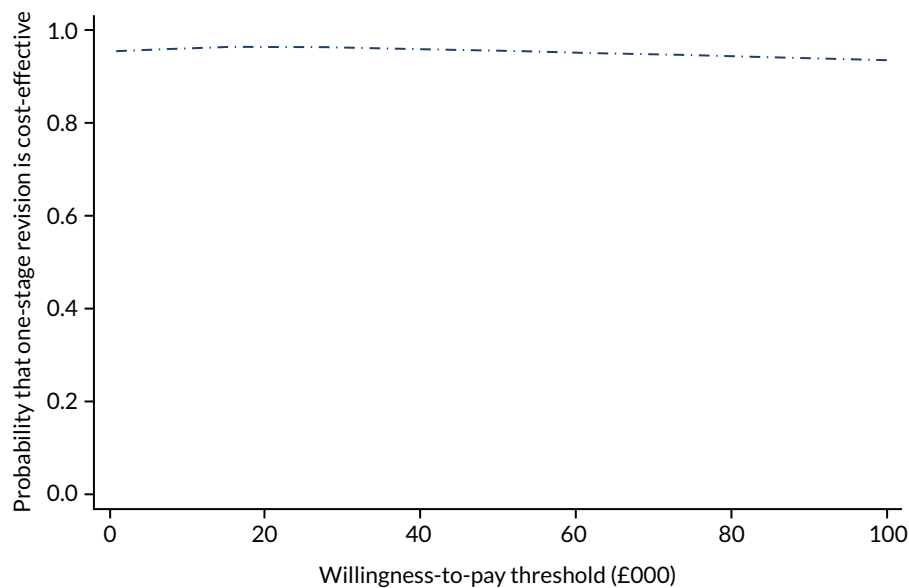MI, multiple imputation; PJI, prosthetic joint infection.

FIGURE 18 The CEAC at 18 months.

Imputation by group was not possible without a substantial loss of information. To gain insight into whether or not using imputation by group was likely to bias the results, both specifications were used in relation to a treating hospital perspective. The iNMBs were similar, and the probability that single stage treatment was cost-effective was 94.8% for the 'by group' model and 94.6% for the 'not by group' model, indicating that the model specification is unlikely to affect the conclusions of the analysis.

We used information from the finance department of a local trust to microcost the revision surgeries for hip prosthetic joint infection. The use of reference costs rather than microcosting to value HRGs reduced the costs in both groups, potentially indicating that reference costs may underestimate the true costs to health-care providers. This was also found by Vanhegan et al.[55] in relation to tariffs.

Cost differences may extend beyond the 18-month trial follow-up. However, the randomised groups had similar hospital costs between 12 and 18 months' follow-up and had similar mean WOMAC and EQ-5D-5L scores at 18 months, and there was also little to suggest a difference in reinfection rates between the groups. Together, these factors suggest that patient costs and outcomes may not differ in the longer term.

In conclusion, the within-trial economic evaluation has shown that the single-stage procedure is the cost-effective option for patients with deep prosthetic hip joint infection.

Appendix 19 Checklist of factors to consider in undertaking and assessing the quality of a discrete choice experiment (using methods described by Lancsar and Louviere[110])

1	Conceptualising the choice process	
	Was a choice rather than ranking, rating task used?	Yes
	What type of choice was used: binary response, pairs, multiple options?	Binary response (from a pair)
	Was a generic or labelled choice used?	Generic (unlabelled)
	Was an opt-out, neither or status quo option included?	No
	If a forced choice was used, was a justification provided?	N/A
	Was the task incentive compatible?	Yes
2	**Attribute selection**	
	How were they derived and validated?	Derived from qualitative interviews and validated in discussions with PPI group
	Was the number of attributes appropriate?	Yes
	Was the coverage appropriate?	Yes
	What form was used: generic or alternative specific?	Generic
	Was price included? If so, was an appropriate payment vehicle used?	No
	Was risk included? If so, was it appropriately communicated?	No
3	**Level selection**	
	How were they derived and validated?	Derived from qualitative interviews and validated in discussions with PPI group
	Was the number of levels per attribute appropriate?	Yes
	Was an appropriate range used?	Yes
	Were the levels evenly spaced?	Yes – derived using qualitative findings
4	**Experimental design**	
	What type of design was used? Full factorial? Fractional factorial? If fractional, which effects are identified: main effects; main effects + higher-order interactions?	Orthogonal main effects, fractional factorial design
	How were the profiles generated and allocated to choice sets?	To avoid order effects, both attributes and choice sets were randomised for profile 1. A moduloarithmetic method was used to generate the second profile
	What are the properties of the design?	Orthogonality, level and utility balance and minimum overlap of levels[148]
	What is the efficiency of the design?	Unknown

4	**Experimental design**	
	Was identification checked (e.g. is the variance-covariance matrix block diagonal)?	Yes
	Was the design blocked into versions? If so, how were choice sets allocated to versions? Were the resulting properties of the versions checked?	No blocking
	Were respondents randomly allocated to versions?	N/A
	How many choice sets were considered per respondent?	16
	If some profiles were implausible – how was implausibility defined and how was it addressed?	N/A
5	**Questionnaire design**	
	Was an appropriate level of background and contextual information provided?	Yes – designed and agreed with the PPI group
	Were the task instructions appropriate?	Yes – approved by PPI group
	Was the medium used to communicate attribute/level information (e.g. words, pictures, multimedia) appropriate?	Yes – approved by PPI group
6	**Piloting**	
	Was coverage of attributes and levels checked?	Yes
	Was understanding and complexity checked?	Yes
	Was the length and timing checked?	Yes
7	**Population/study perspective**	
	Appropriate for research question?	Yes
8	**Sample and sample size**	
	Were inclusion/exclusion criteria explicit?	Yes
	Was sample size appropriate for model estimation?	Yes
9	**Data collection**	
	What recruitment method was used?	Participants had been recruited into the INFORM RCT
	How were data collected (e.g. mail, personal interview, web survey)?	Questionnaire
	What was the response rate?	57/80 (71%) were returned fully complete
	Were incentives used to enhance response rates?	No
10	**Coding of data**	
	Was coding explicitly discussed?	Yes – effects coding used
	Was the coding appropriate for effects to be estimated?	Yes
11	**Econometric analysis**	
	Were the estimation methods appropriate given experimental design and type of choice response?	Yes
	Was the functional form of the indirect utility functions appropriate given the experimental design?	Yes
	Were alternative specific constants included?	No
	Were sociodemographics and other covariates included?	No
	Was goodness of fit considered?	The analysis method provides a pseudo R^2 value that can be used to inform goodness of fit

12	**Validity**	
	Was internal or external validity investigated?	Due to the topic of this programme, and the decision-making associated with this area of health care, there were no revealed preference data to compare with. Responses were in line with expectations and do not suggest any issue with validity of the questions or design
	Were answers for any respondents deleted and, if so, on what basis?	No
13	**Interpretation**	
	Was the interpretation appropriate given coding of data?	Yes
	Were results in line with a priori expectations?	Yes
	Were relative attribute effects compared using a common and comparable metric?	No
14	**Welfare and policy analysis**	
	Was willingness to pay estimated using welfare theoretic compensating variation?	No
	Was probability analysis undertaken?	No
	Were marginal rates of substitution calculated?	No

N/A, not applicable.

Appendix 20 INFORM discrete choice questionnaire

For office use only:

Study ID ⬜⬜⬜⬜⬜ Initials ⬜⬜⬜ DoB ⬜⬜⬜⬜ 19 ⬜⬜

INFORM
Infection: Orthopaedic Management

| **Monitoring Study Questionnaire 18 months** |

Date questionnaire completed: ⬜⬜/⬜⬜/2 0 ⬜⬜

D D M M   Y Y

This booklet contains some questions asking about issues relating to the infection in your hip and your general health. There are no right or wrong answers in this questionnaire. Some of the questions may seem repetitive, but it is important that you try and answer all the questions to the best of your ability.

This questionnaire is likely to take between 10-20 minutes to complete.

Thank you for helping us with this project

These questions ask about how you feel about different surgery options.

- The following questions are slightly different from those you have answered already.
- For a number of good reasons, patients are usually told by their doctors what treatment they will have for infection. We would like to know what you would choose by asking you to imagine you had a choice of treatments in an ideal world.
- The 'side effects' of antibiotics means their unwanted or bad effects.
- If you feel you need support to answer these questions, please telephone your study research nurse or the INFORM office on 01174147867

Instructions

You will be shown a number of pairs of possible surgery options for hip infection. For each pair of options, we would like you to do the following:

1. Read carefully through the surgery options presented in each pair.

2. Imagine that this is the first time you have been offered these two surgery options.

3. Tick <u>one</u> box relating to the surgery option you would choose.

Do not worry that the questions look similar, they are all slightly different. They have been carefully designed to help us work out what is important to people who have had infection.

EXAMPLE – You do not have to answer this question

Imagine this is the first time you are being offered surgery for your infection and you are being asked to choose one of the following surgery options – would you choose "Option 1" or "Option 2"?

OPTION 1		OPTION 2
I take antibiotics and the side effects **don't affect me much** *and* I have **one** operation *and* After my new hip is fitted, **I cannot do most of the things** that I want to do *and* After my surgical treatment starts, it takes **18 months** to get back to the things that I normally do	**OR**	I take antibiotics and the side effects **affect me a lot** *and* I have **two** operations *and* After my new hip is fitted, **I can do everything** that I want to do *and* After my surgical treatment starts it takes **6 months** to get back to the things that I normally do

Please only tick **ONE** box:

OPTION 1   OPTION 2

Imagine this is the first time you are being offered surgery for your infection and you are being asked to choose **one option out of each pair** of the following surgery options...

QUESTION 1: Would you choose "Option A1" or "Option A2"?

OPTION A1		OPTION A2
After my new hip is fitted, **I can do everything** that I want to do *and* After my surgical treatment starts, it takes **3 months** to get back to the things that I normally do *and* I take antibiotics and the side effects **don't affect me much** *and* I have **one** operation	**OR**	After my new hip is fitted, **I can do most of the things** that I want to do *and* After my surgical treatment starts, it takes **6 months** to get back to the things that I normally do *and* I take antibiotics and the side effects **affect me a lot** *and* I have **two** operations

Please only tick **ONE** box:

OPTION A1   OPTION A2

QUESTION 2: Would you choose "Option B1" or "Option B2"?

OPTION B1		OPTION B2
I take antibiotics and the side effects **affect me a lot** *and* After my surgical treatment starts, it takes **3 months** to get back to the things that I normally do *and* I have **two** operations *and* After my new hip is fitted, **I can do most of the things** that I want to do	**OR**	I take antibiotics and the side effects **don't affect me much** *and* After my surgical treatment starts, it takes **6 months** to get back to the things that I normally do *and* I have **one** operation *and* After my new hip is fitted, **I cannot do most of the things** that I want to do

Please only tick **ONE** box:

OPTION B1   OPTION B2

QUESTION 3: Would you choose "Option C1" or "Option C2"?

OPTION C1		OPTION C2
I take antibiotics and the side effects **don't affect me much** *and* After my new hip is fitted, **I cannot do most of the things** that I want to do *and* After my surgical treatment starts, it takes **3 months** to get back to the things that I normally do *and* I have **one** operation	**OR**	I take antibiotics and the side effects **affect me a lot** *and* After my new hip is fitted, **I cannot do anything** that I want to do *and* After my surgical treatment starts, it takes **6 months** to get back to the things that I normally do *and* I have **two** operations

Please only tick **ONE** box:

OPTION C1   OPTION C2

QUESTION 4: Would you choose "Option D1" or "Option D2"?

OPTION D1		OPTION D2
After my new hip is fitted, **I cannot do anything** that I want to do *and* I have **two** operations *and* After my surgical treatment starts, it takes **3 months** to get back to the things that I normally do *and* I take antibiotics and the side effects **affect me a lot**	**OR**	After my new hip is fitted, **I can do everything** that I want to do *and* I have **one** operation *and* After my surgical treatment starts, it takes **6 months** to get back to the things that I normally do *and* I take antibiotics and the side effects **don't affect me much**

Please only tick **ONE** box:

OPTION D1   OPTION D2

QUESTION 5: Would you choose "Option E1" or "Option E2"?

OPTION E1		OPTION E2
I have **one** operation *and* I take antibiotics and the side effects **affect me a lot** *and* After my new hip is fitted, **I cannot do most of the things** that I want to do *and* After my surgical treatment starts, it takes **6 months** to get back to the things that I normally do	**OR**	I have **two** operations *and* I take antibiotics and the side effects **don't affect me much** *and* After my new hip is fitted, **I cannot do anything** that I want to do *and* After my surgical treatment starts, it takes **12 months** to get back to the things that I normally do

Please only tick **ONE** box:

OPTION E1   OPTION E2

QUESTION 6: Would you choose "Option F1" or "Option F2"?

OPTION F1		OPTION F2
I have **two** operations *and* I take antibiotics and the side effects **don't affect me much** *and* After my new hip is fitted, **I cannot do anything** that I want to do *and* After my surgical treatment starts, it takes **6 months** to get back to the things that I normally do	**OR**	I have **one** operation *and* I take antibiotics and the side effects **affect me a lot** *and* After my new hip is fitted, **I can do everything** that I want to do *and* After my surgical treatment starts, it takes **12 months** to get back to the things that I normally do

Please only tick **ONE** box:

OPTION F1   OPTION F2

QUESTION 7: Would you choose "Option G1" or "Option G2"?

OPTION G1		OPTION G2
After my surgical treatment starts, it takes **6 months** to get back to the things that I normally do *and* I have **one** operation *and* I take antibiotics and the side effects **affect me a lot** *and* After my new hip is fitted, **I can do everything** that I want to do	**OR**	After my surgical treatment starts, it takes **12 months** to get back to the things that I normally do *and* I have **two** operations *and* I take antibiotics and the side effects **don't affect me much** *and* After my new hip is fitted, **I can do most of the things** that I want to do

Please only tick **ONE** box:

OPTION G1   OPTION G2

QUESTION 8: Would you choose "Option H1" or "Option H2"?

OPTION H1		OPTION H2
I take antibiotics and the side effects **don't affect me much** *and* I have **two** operations *and* After my new hip is fitted, **I can do most of the things** that I want to do *and* After my surgical treatment starts, it takes **6 months** to get back to the things that I normally do	**OR**	I take antibiotics and the side effects **affect me a lot** *and* I have **one** operation *and* After my new hip is fitted, **I cannot do most of the things** that I want to do *and* After my surgical treatment starts, it takes **12 months** to get back to the things that I normally do

Please only tick **ONE** box:

OPTION H1   OPTION H2

QUESTION 9: Would you choose "Option I1" or "Option I2"?

OPTION I1		OPTION I2
After my new hip is fitted, **I cannot do anything** that I want to do *and* After my surgical treatment starts, it takes **12 months** to get back to the things that I normally do *and* I have **one** operation *and* I take antibiotics and the side effects **don't affect me much**	**OR**	After my new hip is fitted, **I can do everything** that I want to do *and* After my surgical treatment starts, it takes **18 months** to get back to the things that I normally do *and* I have **two** operations *and* I take antibiotics and the side effects **affect me a lot**

Please only tick **ONE** box:

OPTION I1   OPTION I2

QUESTION 10: Would you choose "Option J1" or "Option J2"?

OPTION J1		OPTION J2
After my surgical treatment starts, it takes **12 months** to get back to the things that I normally do *and* I have **two** operations *and* I take antibiotics and the side effects **affect me a lot** *and* After my new hip is fitted, **I cannot do most of the things** that I want to do	**OR**	After my surgical treatment starts, it takes **18 months** to get back to the things that I normally do *and* I have **one** operation *and* I take antibiotics and the side effects **don't affect me much** *and* After my new hip is fitted, **I cannot do anything** that I want to do

Please only tick **ONE** box:

OPTION J1   OPTION J2

QUESTION 11: Would you choose "Option K1" or "Option K2"?

OPTION K1		OPTION K2
After my new hip is fitted, **I can do most of the things** that I want to do *and* I have **one** operation *and* After my surgical treatment starts, it takes **12 months** to get back to the things that I normally do *and* I take antibiotics and the side effects **don't affect me much**	**OR**	After my new hip is fitted, **I cannot do most of the things** that I want to do *and* I have **two** operations *and* After my surgical treatment starts, it takes **18 months** to get back to the things that I normally do *and* I take antibiotics and the side effects **affect me a lot**

Please only tick **ONE** box:

OPTION K1   **OPTION K2**

QUESTION 12: Would you choose "Option L1" or "Option L2"?

OPTION L1		OPTION L2
I have **two** operations *and* After my new hip is fitted, **I can do everything** that I want to do *and* After my surgical treatment starts, it takes **12 months** to get back to the things that I normally do *and* I take antibiotics and the side effects **affect me a lot**	**OR**	I have **one** operation *and* After my new hip is fitted, **I can do most of the things** that I want to do *and* After my surgical treatment starts, it takes **18 months** to get back to the things that I normally do *and* I take antibiotics and the side effects **don't affect me much**

Please only tick **ONE** box:

OPTION L1   **OPTION L2**

QUESTION 13: Would you choose "Option M1" or "Option M2"?

OPTION M1		OPTION M2
I have **one** operation *and* After my surgical treatment starts, it takes **18 months** to get back to the things that I normally do *and* I take antibiotics and the side effects **affect me a lot** *and* After my new hip is fitted, **I can do most of the things** that I want to do	**OR**	I have **two** operations *and* After my surgical treatment starts, it takes **3 months** to get back to the things that I normally do *and* I take antibiotics and the side effects **don't affect me much** *and* After my new hip is fitted, **I cannot do most of the things** that I want to do

Please only tick **ONE** box:

OPTION M1   OPTION M2

QUESTION 14: Would you choose "Option N1" or "Option N2"?

OPTION N1		OPTION N2
After my surgical treatment starts, it takes **18 months** to get back to the things that I normally do *and* I have **two** operations *and* I take antibiotics and the side effects **don't affect me much** *and* After my new hip is fitted, **I can do everything** that I want to do	**OR**	After my surgical treatment starts, it takes **3 months** to get back to the things that I normally do *and* I have **one** operation *and* I take antibiotics and the side effects **affect me a lot** *and* After my new hip is fitted, **I can do most of the things** that I want to do

Please only tick **ONE** box:

OPTION N1   OPTION N2

QUESTION 15: Would you choose "Option O1" or "Option O2"?

OPTION O1		OPTION O2
I have **one** operation *and* I take antibiotics and the side effects **affect me a lot** *and* After my surgical treatment starts, it takes **18 months** to get back to the things that I normally do *and* After my new hip is fitted, **I cannot do anything** that I want to do	**OR**	I have **two** operations *and* I take antibiotics and the side effects **don't affect me much** *and* After my surgical treatment starts, it takes **3 months** to get back to the things that I normally do *and* After my new hip is fitted, **I can do everything** that I want to do

Please only tick **ONE** box:

OPTION O1   OPTION O2

QUESTION 16: Would you choose "Option P1" or "Option P2"?

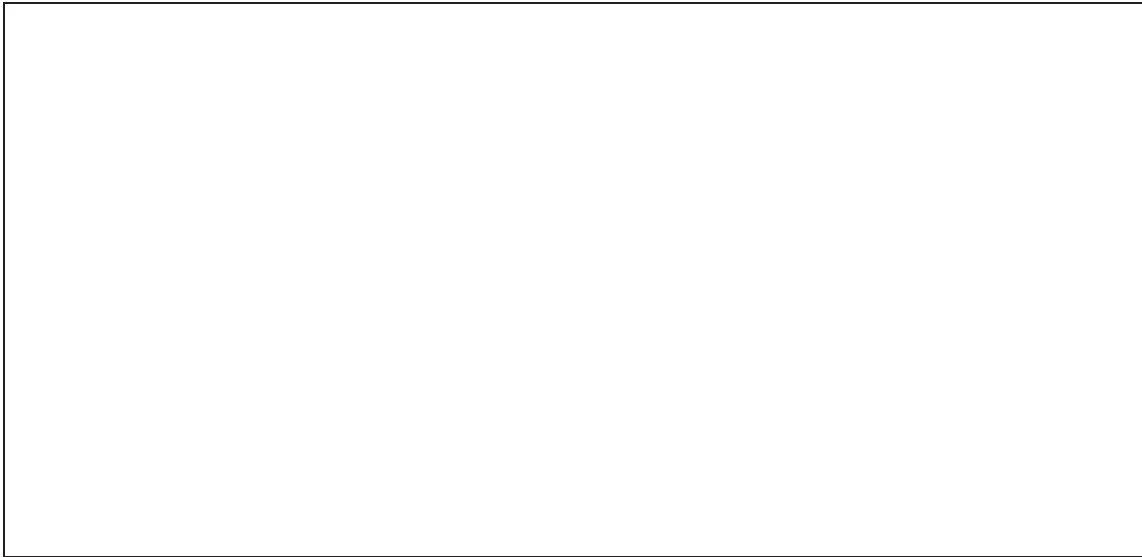| OPTION P1		OPTION P2
I take antibiotics and the side effects **don't affect me much** *and* I have **two** operations *and* After my surgical treatment starts, it takes **18 months** to get back to the things that I normally do *and* After my new hip is fitted, **I cannot do most of the things** that I want to do	**OR**	I take antibiotics and the side effects **affect me a lot** *and* I have **one** operation *and* After my surgical treatment starts, it takes **3 months** to get back to the things that I normally do *and* After my new hip is fitted, **I cannot do anything** that I want to do

Please only tick **ONE** box:

OPTION P1   OPTION P2

> *That's it – you've answered all the questions! Thank you very much for your time.*

Please feel free to add any comments you have about the questionnaire or the project:

Please now return the completed questionnaire in the pre-paid envelope provided.

Appendix 21 British Hip Society symposium

INFORM Symposium British Hip Society

⊃ I N F O R M
Infection: Orthopaedic Management

Friday 6th March 2020

Time: 13.15 – 16.00 / Location: Main Auditorium, ICC Wales

Prosthetic Hip Joint Infection

		Speaker
13.15	Introduction	Prof. Ashley Blom
13.30	Question 1. What is the scale of the problem?	Prof. Ashley Blom
	• Incidence and time trends – NJR data analysis	Dr Erik Lenguerrand
13.45	Question 2. How does it impact on patients' lives?	Prof. Ashley Blom
	• Patient experience of infection and treatments – Qualitative studies	Dr Andrew Moore
	• Surgeons perspective of managing infection – Qualitative studies	Dr Andrew Moore
	• What are patients prepared to accept from treatment? – DCE	Simon Strange
COFFEE BREAK		
14.30	Question 3. Who is most at risk of getting PJI?	Prof. Ashley Blom
	• Risk factors - Systematic reviews	Dr Setor Kunutsor
	• Risk factors - NJR data analysis	Michael Whitehouse
15.00	Question 4. What is the best treatment?	Prof. Ashley Blom
	• DAIR – systematic review	Dr Setor Kunutsor
	• Reinfection outcomes (1vs2 stage) – systematic rv & IPD	Dr Setor Kunutsor / Dr Andrew Beswick
	• Mortality and re-revision (1vs2 stage) – NJR	Dr Erik Lenguerrand
	• RCT (1vs2 stage) – Trial design and delivery	Simon Strange
	• Cost-effectiveness of treatments – Economics plan	Dr Sian Noble
15.50	Summary	
	What have we learned and what is still coming from the INFORM Programme?	Prof. Ashley Blom
16.00	Finish Time	

Speakers:

Prof. Ashley Blom: Head of Bristol Medical School, Professor of Orthopaedic Surgery
Mr Michael Whitehouse: Reader in Trauma and Orthopaedics, Bristol Medical School
Dr Andrew Moore: Research Fellow in Qualitative Health Research, Bristol Medical School
Dr Erik Lenguerrand: Research fellow, Medical statistician, Bristol Medical School
Dr Setor Kunutsor: Research Fellow in Medical Synthesis, Bristol Medical School
Dr Andrew Beswick: Research Fellow, Bristol Medical School
Dr Sian Noble: Senior Lecturer in Health Economics, Bristol Medical School
Mr Simon Strange: Research Programme Manager, North Bristol NHS Trust