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

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ABSTRACT

OBJECTIVES

To determine whether patient reported outcomes improve after single stage versus two stage revision surgery for prosthetic joint infection of the hip, and to determine the cost effectiveness of these procedures.

DESIGN

Pragmatic, parallel group, open label, randomised controlled trial.

SETTING

High volume tertiary referral centres or orthopaedic units in the UK (n=12) and in Sweden (n=3), recruiting from 1 March 2015 to 19 December 2018.

PARTICIPANTS

140 adults (aged ≥18 years) with a prosthetic joint infection of the hip who required revision (65 randomly assigned to single stage and 75 to two stage revision).

INTERVENTIONS

A computer generated 1:1 randomisation list stratified by hospital was used to allocate participants with prosthetic joint infection of the hip to a single stage or a two stage revision procedure.

MAIN OUTCOME MEASURES

The primary intention-to-treat outcome was pain, stiffness, and functional limitations 18 months after randomisation, measured by the Western Ontario and McMasters Universities Osteoarthritis Index (WOMAC) score. Secondary outcomes included surgical complications and joint infection. The economic evaluation (only assessed in UK participants) compared quality adjusted life years and costs between the randomised groups.

RESULTS

The mean age of participants was 71 years (standard deviation 9) and 51 (36%) were women. WOMAC scores did not differ between groups at 18 months (mean difference 0.13 (95% confidence interval −8.20 to 8.46), P=0.98); however, the single stage procedure was better at three months (11.53 (3.89 to 19.17), P=0.003), but not from six months onwards. Intraoperative events occurred in five (8%) participants in the single stage group and 20 (27%) in the two stage group (P=0.01). At 18 months, nine (14%) participants in the single stage group and eight (11%) in the two stage group had at least one marker of possible ongoing infection (P=0.62). From the perspective of healthcare providers and personal social services, single stage revision was cost effective with an incremental net monetary benefit of £11 167 (95% confidence interval £638 to £21 696) at a £20 000 per quality adjusted life years threshold (£1.0; $1.1; €1.4).

CONCLUSIONS

At 18 months, single stage revision compared with two stage revision for prosthetic joint infection of the hip showed no superiority by patient reported outcome. Single stage revision had a better outcome at three months, fewer intraoperative complications, and was cost effective. Patients prefer early restoration of function, therefore, when deciding treatment, surgeons should consider patient preferences and the cost effectiveness of single stage surgery.

TRIAL REGISTRATION

ISRCTN registry ISRCTN10956306.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Prosthetic joint infection is a rare but severe complication of hip replacement and most people require difficult and protracted revision surgery with prosthesis removal, debridement of infected tissue, antibiotic treatment, and replacement

Although revision is widely done as a two stage procedure with replacement delayed for weeks to many months, in an alternative single stage procedure, revision is completed in one operation

In previous case series of people with prosthetic joint infection of the hip, reinfection rates were similar after single stage and two stage revision, but data for patient reported outcomes are required

WHAT THIS STUDY ADDS

INFORM showed no difference in single stage versus two stage revision for prosthetic joint infection of the hip, as assessed by a patient reported measure of pain, function, and stiffness at 18 months

Single stage revision gives quicker restoration of function and relief of pain and is associated with fewer intraoperative complications and is cost effective

Introduction

For people with pain and disability caused by osteoarthritis and other hip conditions, hip replacement can relieve pain and improve function.[1 2] In the UK in 2019, more than 100 000 primary hip replacements were performed to treat diseased or damaged joints.[3 4] In member countries of the Organisation for Economic Co-operation and Development, nearly 1.7 million primary hip

replacements were done in 2015, an average of 224 per 100 000 population.[5] For many people, hip replacements can last over 25 years,[6] but some people experience complications, including prosthetic joint infection, which can result in severe pain, disability, or death.[7 8] Reported rates of prosthetic joint infection within two years of a primary total hip replacement range from 0.8% to 2.1%,[9-12] and about 0.6% of people require implant revision.[13-15] In the US, the lifetime economic burden of treatment is estimated to be approximately $390 000 (£360 000; €405 000).[16]

Treatment of prosthetic joint infection can be challenging for patients and surgeons.[7 17] Most patients require either a single or two stage revision involving prosthesis removal, debridement of infected tissue, antibiotic treatment, and replacement. In a two stage revision, implantation of new prostheses is delayed for a few weeks to many months, permitting localised antimicrobial strategies and infection monitoring. Even with a temporary spacer to maintain some function and leg length, mobility and quality of life are poor between surgeries.[7] An alternative single stage revision, in which implant removal, debridement, and replacement takes place in one operation, is favoured in some centres.[18 19] Although the choice of treatment can be guided by expert opinion,[20] practice has changed with increased use of single stage revision.[13] The main treatment priorities of patients receiving revision for prosthetic joint infection relate to pain, function, and return to normal activities, rather than infection eradication.[21]

Reinfection rates have been shown to be similar between single and two stage revision for treatment of prosthetic joint infection of the hip in large observational studies,[22 23] however, no randomised clinical trials have been done. In the INFORM (INFection ORthopaedic Management) randomised controlled trial, we aimed to determine whether patient reported outcomes are improved 18 months after a single revision compared with two stage revision. We also aimed to assess the cost effectiveness of each treatment in terms of quality adjusted life years and costs from a combined healthcare provider and personal social services perspective, and a wider societal perspective.

Methods

Trial design

INFORM was a pragmatic, parallel group, open label, randomised controlled trial comparing effectiveness and cost effectiveness of single stage with two stage revision to treat prosthetic joint infection of the hip. The protocol and statistical analysis plans are published.[24 25] Conduct and reporting followed CONSORT and CHEERS guidelines (supplementary tables 1 and 2). The UK's National Research Ethics Committee South West-Frenchay (31/12/2014;14/SW/1166) and Sweden's Gothenburg Regional Ethical Review Board (1190-16.2017-02-16) gave ethical approval. All participants provided written informed consent.

Participant selection

Recruitment was from 1 March 2015 to 19 December 2018. Adults (aged ≥18 years) from UK and Swedish tertiary referral centres or orthopaedic units were eligible if they had a prosthetic joint infection of the hip, diagnosed by their treating clinicians, that required revision. Patients were excluded if they were unwilling to undergo either intervention, did not have capacity to consent, or were considered unsuitable for surgery by their treating clinician.

Randomisation and blinding

A concealed, computer generated, 1:1 randomisation list with variable, undisclosed random block sizes (four or six) stratified by hospital was prepared by an independent statistician and accessed through an online system maintained by the clinical trials unit. Randomisation was close to the time of surgery (maximum 12 weeks before) but allowed time for operation planning. Owing to the nature of the intervention and recovery, surgeons and patients were informed of the allocation before surgery.

Interventions

In a single stage revision, patients underwent prosthesis removal, infected tissue debridement, and reconstruction with new prostheses under a single anaesthetic episode. In a two stage revision, patients underwent prosthesis removal, infected tissue debridement under a single anaesthetic episode with insertion of a non-articulating or articulating spacer at the surgeons' discretion. A second stage procedure under a separate anaesthetic episode was performed after an interval at the discretion of the treating surgeon, in which any further debridement required was conducted and a new prostheses inserted. Surgical approach, prostheses, anaesthetics, and antibiotics were according to the treating clinicians' usual practice.

Outcomes

The primary outcome was patient reported pain, stiffness, and function measured by the internationally validated Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC; range 0–100; 100 is best score),[26] at 18 months after randomisation. Eighteen months was chosen because almost a full postoperative recovery in pain and function after revision hip replacement is reported by three months, with a very small additional gain between three and 12 months.[27] Furthermore, in a large UK cohort, the median time between stages of a two stage revision was 105 days (interquartile range 70-173).[13] Secondary outcomes included intraoperative events, serious adverse events (defined in supplementary material methods), WOMAC and its subscales (every three months), Hospital Anxiety and Depression Scale[28] (every six months), Brief Pain Inventory[29] (every six months), Hip dysfunction and Osteoarthritis Outcome Score[30] (every six months), Oxford Hip Score[31] (every six months), 20 metre walk test (at 18 months), and

infection status as described in the supplementary material methods (at 18 months).

Primary outcome questionnaires were self-completed at the clinic or home visit at baseline, and by telephone at follow-up. Secondary outcomes were completed at the clinic or home visit at baseline, and by postal questionnaires at follow-up. A walk test was also conducted at 18 months in an outpatient hospital clinic. Information on complications and hospital readmissions were collected from hospital medical records.

The economic analysis outcome was the quality adjusted life year[32] at 18 months follow-up, which was calculated using the EuroQol-5D-5L.[33] This assessment was completed at baseline (clinic or home visit), at three months by telephone, and at months six, 12, and 18 by postal questionnaires. Resources were valued in 2018-19 UK prices. Methods used to estimate utility values, and measure and value resources are described in the supplementary material methods and supplementary table 3.

Sample size

The WOMAC score standard deviation in patients with prosthetic joint infection of the hip is between 18 and 25.[34 35] We calculated that a sample size of 128 participants would provide 80% power to show a 10 point difference in WOMAC score, equivalent to 0.5 standard deviation, between single and two stage revision. Assuming a two sided type I error of 5% and 13% attrition,[36] we estimated that a sample of 148 participants would need to be randomly assigned.

Statistical analysis

Statistical analyses are described in the supplementary material. Statistical and cost effectiveness analyses were done with Stata/MP version 15.1 (StataCorp). The study was analysed by intention-to-treat methods. The primary analysis was a two level linear model regressing the repeated measures of total WOMAC score on allocation group, time of assessment, their interaction, and adjusted for hospital and baseline total WOMAC score as fixed effects (measurements nested within patients modelled as random effects).[37] The mean total WOMAC score at 18 months after randomisation of each allocation group and their differences were assessed by linear combination of the parameters from this model, with group differences at other time points estimated from the same model. Prespecified sensitivity analyses of the primary outcome were conducted (supplementary material methods): adjustment for imbalanced variables at baseline between randomised groups; a multiple imputation chained equation strategy to account for participants with missing data; a combined imputation and adjustment analysis; adjustment to account for operating surgeon modelled as fixed effects; adjustment to further consider patient and surgical characteristics; tobit analysis to account for WOMAC score ceiling effect; and an analysis restricted to centres where fewer than 50% of two stage procedures were performed using a custom made articulating spacer where cemented implants were used as a spacer but loosely fixed to facilitate revision at second stage surgery if required.[38]

Cost effectiveness analysis

Cost effectiveness analyses (healthcare provider and personal social services, and societal perspective) compared the groups that were randomised over 18 months (the time horizon). Costs and outcomes after one year from randomisation were discounted at 3.5%.[32] Resource items were grouped into categories and summed for each participant, and mean resource use was calculated by category and trial group. Each item's cost was calculated by multiplying the resource use (see supplementary table 25 for resource use categories) by its unit cost and were summed for each participant. To account for missing data, multiple imputation by chained equations using predictive mean matching was used (supplementary material methods). Unadjusted costs associated with healthcare delivered at the treating hospital (treating hospital perspective) were estimated for three time periods (0 to 6 months; 6 months to 1 year; 12 to 18 months). Unadjusted mean utility values were calculated by time point and trial group.

Adjusted mean costs and quality adjusted life years by trial group and differences in adjusted mean costs and quality adjusted life years over the 18 month period were estimated using the seemingly unrelated regressions method, which accounts for the correlation between costs and quality adjusted life years.[39] Costs and quality adjusted life years were adjusted for hospital site, and quality adjusted life years were also adjusted for baseline utility.

We calculated the incremental net monetary benefit statistic, representing the value of the intervention in monetary terms where a willingness-to-pay threshold for a unit of benefit is known, using seemingly unrelated regression. The UK National Institute for Health and Care Excellence willingness-to-pay threshold of £20 000 was used.[32]

Sample uncertainty within cost effectiveness estimates was investigated exploratory using cost effectiveness acceptability curves[40] calculated from the seemingly unrelated regression at different willingness-to-pay per quality adjusted life year thresholds (£0–100 000, in £1000 increments).

As described in the supplementary material methods, sensitivity analyses were undertaken to account for methodological uncertainty or assumptions made during the study and analysis.

Patient and public involvement

In December 2010, February 2011, and September 2011, the planned research was discussed with the University of Bristol Patient Experience Partnership in Research (PEP-R) group, comprising nine people with musculoskeletal conditions. Use of National Institute for Health and Care Research (NIHR) INVOLVE guidance ensured appropriate organisation of patient

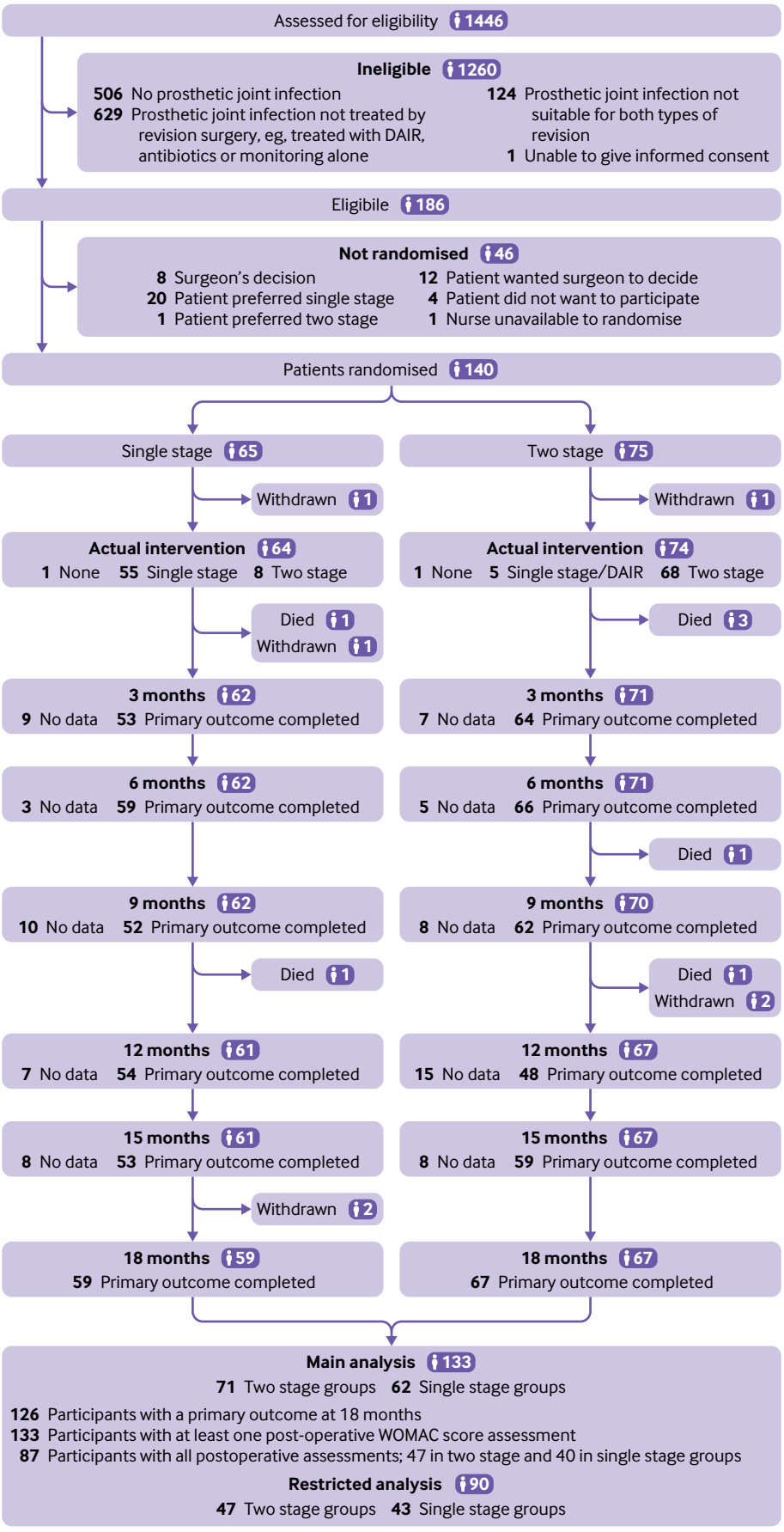

Fig 1 | CONSORT trial profile. DAIR=debridement, antibiotics and implant retention; WOMAC=Western Ontario and McMasters Universities Osteoarthritis Index

Table 1 | Participant baseline characteristics by randomised group. Data are number (%) of participants unless otherwise specified

Baseline characteristics	Single stage revision surgery(n=65)	Two stage revision surgery(n=75)
Characteristics		
Mean (SD) age at inclusion (years)	70 (9)	72 (10)
Mean body mass index	29 (7)	29 (5)
Female sex	20 (31)	31 (41)
Previous treatment for infection:		
Antibiotics only	44 (68)	41 (55)
One surgery	14 (22)	24 (32)
Two surgeries	3 (5)	7 (9)
Three or more surgeries	4 (6)	3 (4)
Previous joint replacement procedure as primary procedure	48 (74)	58 (77)
Indication for primary procedure:		
Acute trauma	3 (5)	11 (15)
Another indication	1 (2)	3 (4)
Osteoarthritis	35 (54)	38 (51)
Osteoarthritis and another indication	2 (3)	1 (1)
Unknown indication	7 (11)	5 (7)
Primary procedure:		
Cemented total hip replacement	19 (29)	27 (36)
Uncemented total hip replacement	11 (17)	9 (12)
Hybrid total hip replacement	10 (15)	9 (12)
Hemi-arthroplasty	0	6 (8)
Resurfacing	1 (2)	1 (1)
Other	0	2 (3)
Unknown	7 (11)	4 (5)
Previous joint replacement procedure as revision procedure	17 (26)	17 (23)
Indication for revision:		
Adverse soft tissue reaction	0	2 (3)
Aseptic loosening	1 (2)	2 (3)
Component mismatch	0	1 (1)
Dislocation/subluxation	5 (8)	3 (4)
Implant fracture	0	1 (1)
Pain	1 (2)	1 (1)
Peri-prosthetic fracture	1 (2)	1 (1)
Several revision indications	4 (6)	4 (5)
Wear of acetabular component	2 (3)	0 (0)
Other revision indication	3 (5)	2 (3)
Last revision procedure		
Cemented total hip replacement	4 (6)	6 (8)
Uncemented total hip replacement	7 (11)	3 (4)
Hybrid total hip replacement	2 (3)	1 (1)
Unknown	4 (6)	7 (9)
Mean baseline outcome measures		
WOMAC global	45 (25)	41 (23)
WOMAC pain subscale	48 (27)	47 (26)
WOMAC function subscale	44 (26)	39 (25)
WOMAC stiffness subscale	50 (30)	45 (29)
BPI pain severity	5 (3)	5 (3)*
BPI pain interference	6 (3)	6 (3)†
HADS anxiety	8 (5)	7 (4)†
HADS depression	8 (5)	7 (4)†
HOOS quality-of-life scale	29 (23)	24 (21)†
Oxford Hip Score	19 (13)	17 (12)†
Completed walking test:		
Completed	41 (63)	44 (59)
Incomplete	24 (37)	31 (41)
Median (IQR) time walking test (minutes)	26 (18-38)‡	30 (23-44)§

BPI=Brief Pain Inventory; HADS=Hospital Anxiety and Depression Scale; HOOS=Hip Disability and Osteoarthritis Outcome Score; IQR=interquartile range; SD=standard deviation; WOMAC=Western Ontario and McMasters Universities Osteoarthritis Index.
*n=73.
†n=74.
‡n=41.
§n=44.

and public involvement. With training and support from research staff and our patient involvement co-ordinator (AB), PEP-R group members were familiar with research design and conduct. The PEP-R group acknowledged that although relatively few people develop a prosthetic joint infection, the research was important and highlighted the need for feasibility work to assess the acceptability of randomisation to patients and surgeons.

Within the programme, a dedicated patient forum of five people with experience of prosthetic joint infection met on 33 occasions between 2014 and 2021 to discuss issues relating to prosthetic joint infection. Important contributions have related to the design of patient recruitment and information literature, research processes, questionnaires, and identification of outcomes of importance to patients. People from this forum and the PEP-R group will be involved in supporting dissemination strategies, including the making of a YouTube video for dissemination to a lay audience.

Results

At 15 high volume tertiary referral centres or orthopaedic units (12 in the UK, three in Sweden), 1446 patients were screened and 140 patients were randomly assigned to single stage (n=65) or two stage (n=75) revision (fig 1, supplementary tables 4 and 5). Most ineligible patients did not have a prosthetic joint infection (n=506, 35%) or require complete revision (n=629, 43%). The most common reasons that eligible patients were not randomly assigned (n=46) were patient preference for single stage revision (n=20, 43%) or patient request for their surgeon to choose the procedure (n=12, 26%). At 18 months after randomisation, 126 (90%) of 140 patients had completed a primary outcome and 133 (95%) of 140 patients with at least one postoperative WOMAC score were included in the main analysis.

Group baseline characteristics were generally balanced, mean age was 71 years (standard deviation 9) and 51 (36%) of 140 patients were women; however, patients receiving a single stage revision were more likely to be male, to be of American Society of Anesthesiologists classification I or II, and to have previously received non-surgical management (table 1, supplementary table 6). No major differences were reported between groups in the number of organisms cultured, culture negative infections, organism types, presence of sinus tract, or other characteristics (table 2, supplementary table 7).

In the single stage group, 55 (85%) of 65 patients received their assigned intervention, eight received a two stage procedure and one was not revised (fig 1). Four patients withdrew during follow-up and two died. In the two stage group, 68 (91%) of 75 patients received their assigned intervention, five received an alternative revision procedure and one was not revised. Three patients withdrew during follow-up and five died. The median time between stages was 3.7 months (interquartile range 2.6-6.1).

Participants received an intervention within three months of randomisation except for eight (12%) of 65 participants in the single stage group and 10 (13%) of

Table 2 | Participant surgical characteristics by randomised group. Data are number (%) of participants, unless otherwise specified

Surgical characteristics	Single stage revision surgery (n=65)	Two stage revision surgery (n=75)
Actual first surgery:		
Single stage	55 (85)	3 (4)
Two stage	8 (12)	68 (91)
Other	0 (0)	2 (3)
No surgery	2 (3)	2 (3)
Median (IQR, range) time between stages (months)	NA	3.7 (2.6-6.1), (0.5-15.9)
Bacteria culture at baseline:		
Monomicrobial culture	38 (59)	51 (68)
Negative culture	6 (9)	4 (5)
Polymicrobial culture	17 (26)	16 (21)
Unknown	4 (6)	4 (5)
Presence of sinus tract at baseline:		
No sinus tract	44 (68)	51 (68)
Presence of a sinus tract	21 (32)	24 (32)
Definitive fixation method used in revision for prosthetic joint infection:		
No surgery or other type of surgery	2 (3)	4 (5)
Cemented single stage	25 (39)	2 (3)
Uncemented single stage	14 (22)	0 (0)
Hybrid single stage	16 (25)	1 (1)
Two stage with no second stage	1 (2)	3 (4)
Two stage with no second stage: CUMARS	0 (0)	13 (17)
Cemented second stage of two stage	0 (0)	7 (9)
Uncemented second stage of two stage	3 (5)	29 (39)
Hybrid second stage of two stage	4 (6)	16 (21)
Fixation used in first stage of two:		
No surgery or other type of surgery	2 (3)	4 (5)
Single stage	55 (85)	3 (4)
Excision	2 (3)	8 (11)
Cement hemiarthroplasty spacer	3 (5)	23 (31)
Static spacer	3 (5)	10 (13)
Implant articulating spacer	0 (0)	2 (3)
Kiwi articulating spacer	0 (0)	25 (33)
Mean (SD) duration of stage (min):		
Single stage	243 (71)	179 (19)
First stage of two	186 (55)	190 (65)
Second stage of two	177 (45)	161 (57)
Overall median (IQR, range) length of time in hospital since admission (days)	17 (12-27), (0-304)	24 (14-34), (0-439)
Incomplete surgical treatment:		
Completed	62 (95)	55 (73)
Only first stage of two stage	1 (2)	3 (4)
Two stage performed as CUMARS	0 (0)	13 (17)
Other surgical treatment	0 (0)	2 (3)
No surgical treatment	2 (3)	2 (3)
Required unplanned surgery:		
No unplanned surgery	51 (79)	65 (87)
More unplanned surgery	14 (22)	10 (13)
Median (IQR, range) No of procedures recorded	1 (1-1), (0-5)	2 (1-2), (0-5)
Last recorded surgery is an excision:		
No	65 (100)	74 (99)
Yes	0 (0)	1 (1)

[i] CRP=C reactive protein; CUMARS=custom made articulating spacer; ESR=erythrocyte sedimentation rate; IQR=interquartile range; NA=not applicable; SD=standard deviation.

75 participants in the two stage group. All but two of these participants in the single stage group and two in the two stage group eventually received revision surgery.

Primary outcome measure

No evidence indicated superiority of the single stage over the two stage revision at 18 months after randomisation for the total WOMAC score. The mean single stage WOMAC score was 75.21 (95% confidence interval 66.47 to 83.96) and the mean two stage score was 75.67 (66.94 to 84.40); the mean difference between groups was 0.13 (−8.20 to 8.46), P=0.98 (fig 2, table 3, supplementary table 8 and supplementary fig 1). Sensitivity analyses supported the main primary outcome analysis with: adjustment for imbalanced variables at baseline; 14 missing assessments imputed; adjustment plus imputation; adjustment for patient and surgical characteristics; adjustment accounting for operating surgeon modelled as fixed effects; tobit analysis to account for WOMAC score ceiling effect; and with centres where fewer than 50% of two stage procedures were done using a custom made articulating spacer (table 3, supplementary table 9 and supplementary fig 2).

Secondary outcomes

At three months after randomisation, the single stage group had a better total WOMAC score than did the two stage group (mean difference between groups 11.53 (3.89 to 19.17), P=0.003), but not from six months onwards (fig 2 and supplementary table 10). No differences in WOMAC subscales at any time point, or Hip dysfunction and Osteoarthritis Outcome Score,[30] Oxford Hip Score, Brief Pain Inventory interference or severity, or Hospital Anxiety and Depression Scale at 18 month follow-up were reported (fig 3, supplementary tables 11-19 and supplementary figs 3-20). Findings were similar in sensitivity analyses. More participants in the single stage group completed the walk test successfully at 18 months than did those in the two stage group (47 (78%) of 60 *v* 41 (61%) of 67) but walking speeds were similar (supplementary table 20 and 21 and supplementary figs 21–24).

Weak evidence suggests a lower rate of complications in the single stage group (27 (42%) of 65) compared with the two stage group (43 (57%) of 75), P=0.04 (table 4 and supplementary tables 22 and 23). Stronger evidence was reported of lower rates of intraoperative events in the single stage (5 (8%) of 65) compared with the two stage group (total of intraoperative events across both surgeries, 20 (27%) of 75), P=0.01; of which these were predominantly fractures, ranging from calcar cracks to femoral shaft fractures. Risks of readmission to hospital or reoperation owing to prosthetic joint infection, the surgery, or another cause, were similar in the two groups. In the single stage group, 11 (17%) of 65 participants had a serious adverse event compared with 16 (21%) of 75 participants in the two stage group (P=0.51). Over the 18 month follow-up, five people died in the two stage group and two people died in the single stage group (P=0.45).

At 18 months, nine (14%) of 65 participants in the single stage group and eight (11%) of 75 participants in the two stage group (P=0.62) had at least one marker of possible infection. Four (6%) of 65 participants in the single stage and four (5%) of 75 participants in

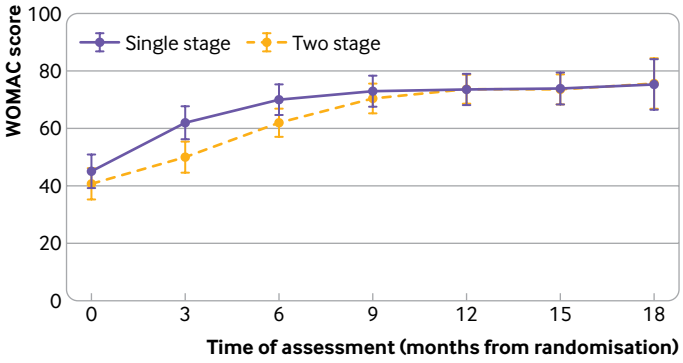

Fig 2 | Mean (95% confidence interval) total WOMAC score after single stage and two stage revision for prosthetic joint infection of the hip during 18 months of follow-up. WOMAC=Western Ontario and McMasters Universities Osteoarthritis Index

the two stage group received antibiotics 15-18 months after randomisation.

Cost effectiveness analysis

Data collection of resource use differed in Sweden; therefore, the primary economic analysis was conducted on 128 participants (n=60 single stage; n=68 two stage) randomly assigned in UK hospitals (ie, 91% of the total sample). Complete resource use and costs from treating hospitals were available for 114 (89%) participants, reducing to 41% from healthcare provider and personal social services and 36% from societal perspectives due to missing questionnaires. Missing data information for variables included in the multiple imputation model (n=128) is shown in supplementary table 24.

Resources used by the UK cohort over the 18 months varied (supplementary table 25). Mean theatre time was 76 min longer for patients in the two stage revision group. This group also spent a longer time in recovery, in high dependency or intensive treatment units, and in hospital overall, compared with the single stage group. These participants also had a greater mean number of subsequent inpatient stays, emergency department attendances, district nurse home visits, nights in residential care homes, home care visits, took more paid leave, and lost more hours from usual activities. Patients randomly assigned to a single stage procedure had more primary care nurse visits, took a greater mean number of hours of unpaid leave, and lost more working hours in terms of permanently giving up work and reduction in hours worked.

EuroQol-5D-5L utility values for the UK cohort showed that participants randomly assigned to the single stage procedure had a gradual improvement from three months (supplementary table 26). For people assigned to the two stage procedure, the improvement began at six months. The unadjusted mean costs of all treating hospital surgical admissions became similar between the trial groups in the last six months of follow-up (supplementary table 27).

The total adjusted mean costs for the UK cohort over the 18 month follow-up in the single stage group were less than in the two stage group from the healthcare provider and personal social services perspective, £36 256 versus £46 312, a cost difference of −£10 055 (−£19 568 to −£542; table 5). This difference reduced slightly from the societal perspective, £51 420 versus £60 870, a cost difference of −£9450 (−£22 855 to £3956). UK participants in the single stage group had a greater number of adjusted mean quality adjusted life years than did those in the two stage group, 0.75 versus 0.69, a difference of 0.06 (−0.07 to 0.18). The incremental net monetary benefit of single stage compared with two stage was £11 167 (£638 to £21 696) for healthcare provider and personal social services perspective and £10 589 (−£3855 to £25 033) for societal perspective at £20 000 per quality adjusted life year threshold.

Cost effectiveness acceptability curves showed high certainty (supplementary fig 25), and at the UK NICE willingness-to-pay threshold of £20 000 per quality adjusted life year, the probability that the single stage revision was the cost effective group was 98% for healthcare provider and personal social services and 92% for the societal perspective. Sensitivity analyses (supplementary table 28) did not reduce the probability that the single stage procedure was cost effective.

Table 3 | Difference in WOMAC scores between single and two stage (reference) groups at 18 months after randomisation

Analysis*	No of patients	Mean difference (95% CI)	P value
Primary ITT analysis	133	0.13 (−8.20 to 8.46)	0.98
Sensitivity analyses:			
ITT adjusted	133	−1.51 (−10.07 to 7.04)	0.73
ITT with imputation	140	−0.01 (−9.82 to 9.81)	0.99
ITT adjusted and imputed	140	−1.24 (−11.22 to 8.74)	0.81
ITT adjusted model including operating surgeon	133	−0.29 (−8.83 to 8.24)	0.95
ITT tobit	133	−0.34 (−8.69 to 8.01)	0.94
Hospitals with <50% CUMARS	90	−1.26 (−11.69 to 9.17)	0.81

CI=confidence interval; CUMARS=custom made articulating spacer, ITT=intention to treat; WOMAC=Western Ontario and McMasters Universities Osteoarthritis Index.
*Primary ITT analysis is a two level linear model adjusted for intervention, time of assessment, interaction terms between intervention and assessment time, baseline WOMAC score, hospital, and clustering of repeated WOMAC measures within participants 3-18 months after randomisation. ITT adjusted model is a primary analysis with further adjustment for sex, previous surgical management of prosthetic joint infection, and American Society of Anesthesiologists grade. ITT with imputation is a primary analysis with 33 imputed sets derived with multiple imputation by chained equations and results combined using Rubin's rules. ITT adjusted and imputed is an imputed analysis with further adjustment for sex, previous surgical management of prosthetic joint infection, and American Society of Anesthesiologists grade. ITT adjusted model including operating surgeon is a two level linear model adjusted for intervention, time of assessment, interaction terms between intervention and assessment time, baseline WOMAC score, hospital, clustering of repeated WOMAC measures within participants 3-18 months after randomisation, and operating surgeon modelled as fixed effects. ITT tobit is a primary analysis with two level tobit model regressing the non-imputed sample to account for WOMAC score ceiling effect. Hospitals with <50% CUMARS is a primary analysis in participants from hospitals that performed <50% of their two stage procedures with the CUMARS approach.

Discussion

Principal findings

In this randomised comparison, single stage revision was not superior to two stage revision for treatment of prosthetic joint infection of the hip as assessed at 18 months with the patient reported WOMAC score. However, a greater improvement in the WOMAC scores was noted in the single stage group at three months, implying quicker recovery, and a lower risk of intraoperative complications, especially fractures. Single stage revision was also associated with lower costs and higher quality adjusted life years than two stage revision and hence, was the cost effective option

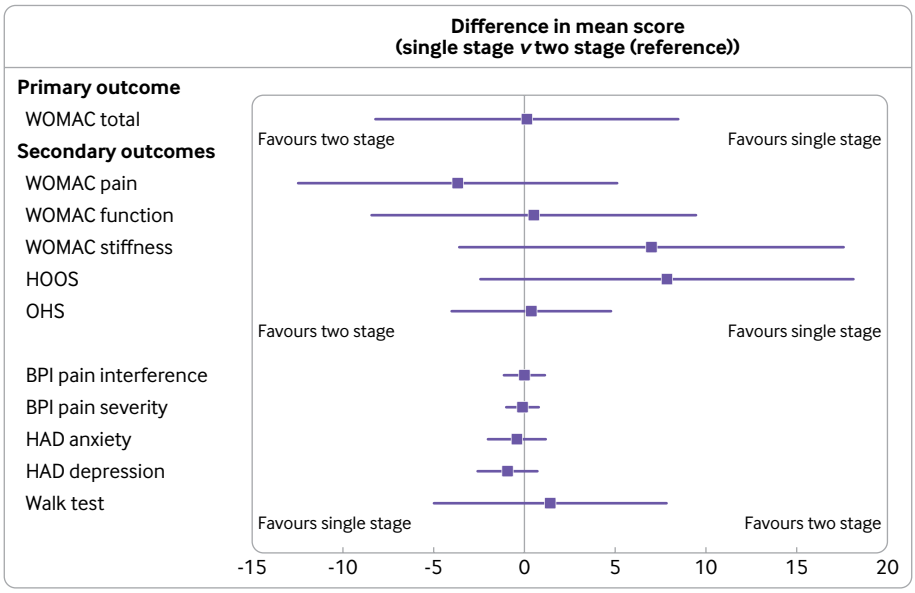

Fig 3 | Mean differences (95% confidence intervals) in primary and secondary outcomes between single stage and two stage revision for prosthetic joint infection of the hip at 18 months after randomisation. BPI=Brief Pain Inventory; HADS=Hospital Anxiety and Depression Scale; HOOS=Hip Disability and Osteoarthritis Outcome Score; OHS=Oxford Hip Score; WOMAC=Western Ontario and McMasters Universities Osteoarthritis Index

with the two hospital stays of a two stage revision being the major factor. The observed quality adjusted life year difference equates to an extra 33 days in best imaginable health during the 18 months for the single stage group. The greater use of district nurses and home care workers indicates that the patients in the two stage group were less able to self-care and leave home after surgery.

Comparison with previous studies

In previous case series of people with prosthetic joint infection of the hip, reinfection rates were similar after single stage and two stage revision at about 8% or less,[22 41] but data for patient reported outcomes are very scarce.[22] A meta-analysis of cohort studies at the individual patient data level of 1856 patients also found no difference in re-infections after either strategy, despite a greater proportion of patients in the single stage group having a previous prosthetic joint infection or sinus compared with the two stage group.[23] Findings were consistent after adjustment for age, sex, previous hip surgery, comorbidities, and difficult-to-treat organisms.

Non-randomised studies have suggested that two stage revision is 1.6-1.7 times more costly than single stage revision.[42 43] We showed the difference in costs from a healthcare provider and personal social services perspective to be 1.3 times greater and from a societal perspective, 1.2 times greater, for two stage compared with single stage revision. The smaller difference could result from selection bias in previous studies because surgeons might have performed a two stage revision on selected patients, for example, those with sinus.

Strengths and limitations of study

Our study had limitations. The primary outcome was not infection eradication and the INFORM randomised controlled trial would have had to have been unfeasibly large to focus on this outcome; but this question might be quantifiable in meta-analysis with additional trials. However, we used a validated core patient reported outcome measure to reflect the overall experience of surgery to treat prosthetic joint infection which our patient forum preferred and is consistent with results of a discrete choice experiment.[21] Although further follow up beyond 18 months might have identified later complications and infections, WOMAC scores and EuroQol-5D-5L had plateaued and were similar between groups. Furthermore, randomised groups had similar hospital costs between 12 month and 18 month follow-ups, and we believe that the care pathway or patient outcomes will unlikely be different between the two groups beyond the 18 month time point. Diagnostic guidelines were in existence while the INFORM randomised controlled trial was in development,[44 45] with regular substantial changes.[46 47] We included

Table 4 | Rates of complications in groups randomised to single or two stage revision for prosthetic joint infection. Data are number (%) of participants, unless otherwise specified

Complication	Single stage revision surgery (n=65)	Two stage revision surgery (n=75)	P value
Death	2 (3)	5 (7)	0.45
Serious adverse event	11 (17)	16 (21)	0.51
Complication of surgery	27 (42)	43 (57)	0.04
Intraoperative event	5 (9)	20 (27)	0.01
Readmission to hospital	22 (34)	31 (41)	0.47
Reoperation	10 (15)	20 (27)	0.08
Readmission to hospital owing to prosthetic joint infection	10 (15)	17 (23)	0.33
Reoperation owing to prosthetic joint infection	6 (9)	9 (12)	0.55
Possible prosthetic joint infection at 15-18 months	9 (14)	8 (11)	0.62
Prescribed antibiotics at 15-18 months	4 (6)	4 (5)	—

Table 5 | Cost effectiveness results for the UK cohort. Data are mean (95% confidence interval), unless otherwise stated

Perspective and revision stage	No of participants	Adjusted costs* (£)	Adjusted QALY*†	Incremental costs	Incremental QALYs	Incremental NMB (£) at £20 000/QALY
Healthcare provider and personal social services 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)
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)

NMB=net monetary benefit; QALY=quality adjusted life year. £1.0 equates to $1.1 and €1.4.
*All variables are adjusted for hospital. Additionally, QALYs are adjusted for baseline utility score.

patients with prosthetic joint infection diagnosed according to the practice of treating surgeons and multidisciplinary teams rather than a trial specific definition of prosthetic joint infection or the diagnostic guidelines, partly because some of the included tests were not routinely used in the INFORM centres, which reflected contemporary UK and Swedish practice. Considering the European Bone and Joint Infection Society criteria,[47] patients included in the randomised controlled trial were most probably those who had an infection confirmed rather than infection likely. The preference of some surgeons to insert less well fixed hip replacement prostheses at the first stage of a two stage revision and hence, performing a two stage procedure that might never require a second stage,[38] added heterogeneity to this group but reflected the pragmatic nature of the trial. In our sensitivity analysis, primary outcome results were consistent when accounting for this heterogeneity.

Missing questionnaire data were a limitation for the cost effectiveness analysis from personal and societal perspectives; although, because the rate of missing data was similar between groups, any biases resulting from missing data were unlikely to have a substantial impact on the results.

A strength of this pragmatic randomised controlled trial is that patients were not excluded based on the organisms causing the infection or adverse clinical features, such as the presence of a sinus tract. This method was consistent with the findings of the largest observational study to date on the topic, which showed that these factors had no clear influence on outcome.[23] Our trial reports both the final outcome and the patient journey. Qualitative research has shown how severely this journey affects patients[7 48] and thus, quantifying these differences is a valuable outcome of this trial.

Conclusions

The INFORM randomised controlled trial showed that single stage revision is not superior to two stage revision for treatment of prosthetic joint infection of the hip, as assessed by the WOMAC measure comprised of pain, function, and stiffness at 18 months. Single stage surgery gives quicker restoration of function and relief of pain, factors which are of high importance to patients, is associated with fewer intraoperative complications and is cost effective. We recommend an increased use of this choice of intervention in appropriate patients.

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Ethical approval: This study was approved in the UK by National Research Ethics Committee South West-Frenchay (31/12/2014;14/SW/1166) and in Sweden by Gothenburg Regional Ethical Review Board (1190-16.2017-02-16).

Data sharing: The datasets generated in the INFORM randomised clinical trial will be available in the University of Bristol Research Data Repository (https://data.bris.ac.uk/data/). Data will be available within six months following publication. Access to the data will be restricted to ensure that data are only made available to bona fide researchers for ethically approved research projects, on the understanding that confidentiality will be maintained and after a data access agreement has been signed by an institutional signatory.

The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Dissemination to participants and related patient and public communities: We are actively involving the award winning Patient Experience Partnership PPI group and INFORM patient forum in dissemination plans. These include a YouTube video, which we have commissioned, tweets from the University of Bristol Medical School and Musculoskeletal Research Unit accounts, and a summary to be sent to INFORM participants when the study is published. A plain English summary of the INFORM programme (including the INFORM RCT) as submitted to NIHR is included in the supplementary material.

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Web appendix: Supplemental material