# Surgery for Hip Infection Project

## A Multi-Centred, Randomised Trial to compare 1-Stage with 2-Stage Revision Surgery for Prosthetic Hip Joint Infection

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<td>References section updated. Specific references to study sites removed. Pre-op questionnaires changed.</td>
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## Approvals

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## Authorised by:

Prof. Ashley Blom  
Signature:  
Chief Investigator  
Date:
General Information

This protocol describes the INFORM trial and provides information about procedures for entering participants. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the trial. Problems relating to this trial should be referred, in the first instance, to the Chief Investigator.

This trial will adhere to the principles outlined in the NHS Research Governance Framework for Health and Social Care (2nd edition). It will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate.

Trial Co-ordinating Centre

For general queries, supply of trial documentation, and collection of data, please contact:

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**FOR RANDOMISATIONS, PLEASE ACCESS:**

[https://www.brtrandomisation.bristol.ac.uk/cgibin/cgi?recruit](https://www.brtrandomisation.bristol.ac.uk/cgibin/cgi?recruit)

You will need to enter the following information:

- Your 6-digit PIN
- Participant ID (5 Digits)
- Centre
- Eligibility for 1 AND 2-stage surgery
- Study consent has been taken and patient willing to participate
- WOMAC score from pre-operative primary questionnaire
- Participant has agreed to randomization
Trial Management Group

Chief Investigator: Ashley Blom¹,³
Orthopaedic Surgeon: Michael Whitehouse¹,³
Microbiologist: Alasdair MacGowan³
Qualitative Methodologist: Rachael Gooberman-Hill¹
Trialist: Athene Lane²
Heath Economist: Sian Noble²
Statistician: Erik Lenguerrand¹
Patient and Public Involvement Coordinator: Amanda Burston¹

Affiliations

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Sponsor

North Bristol NHS Trust will act as main Sponsor for this trial. Delegated responsibilities will be assigned to the NHS Trusts taking part in this trial.

Contact Name: Helen Lewis, Lead Research Nurse.

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Funding

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## Protocol Synopsis

<table>
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<th>Title</th>
<th>A multi-centred, randomised trial to compare 1-stage with 2-stage revision surgery for prosthetic hip joint infection.</th>
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<td>Primary Objective</td>
<td>To compare patient reported outcomes at 18–months after randomisation, as measured by WOMAC score of hip pain, function and stiffness.</td>
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<td>Study Design</td>
<td>Multi-centred, two armed, parallel group, unblinded, randomised, superiority trial with 1:1 treatment allocation. With embedded qualitative and monitoring studies.</td>
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<td>Population</td>
<td>Patients with deep prosthetic hip joint infection</td>
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</table>
| Interventions | 1. 1-stage revision surgery  
2. 2-stage revision surgery |
| Number of Patients | 142 randomised  
Approximately 80 non-randomised (monitoring group)  
TOTAL = 222 participants  
Those who are eligible but unwilling to take part in the randomised trial will be asked to take part in the monitoring study. |
| Inclusion Criteria | 1. Age 18 or above  
2. A clinical diagnosis of prosthetic hip joint infection  
3. Require revision surgery (1-stage or 2-stage) for prosthetic hip joint infection, in the opinion of the treating orthopaedic surgeon(s) |
| Exclusion Criteria | 1. Unable or unwilling to undergo either 1-stage or 2-stage revision surgery  
2. Lack capacity to give written informed consent for research |
| Outcome Assessments / Schedule of Visits | Randomised participants:  
- Consent visit\(^1\)  
- Pre-Operative Assessment visit\(^1\)  
- Post-Operative Qualitative Interviews\(^1\)  
- 3 month phone questionnaire  
- 6 month phone\(^2\) and postal questionnaires  
- 9 month phone questionnaire  
- 12 month phone\(^2\) and postal questionnaires  
- 15 month phone questionnaire  
- 18 month phone questionnaire\(^1\), postal questionnaire and research visit  
- End of Study Qualitative Interviews  
\(^1\)Monitoring participants’ assessments |
| Duration of Follow-up | 18 months |

NOTE: Assessments will occur at the above time-points from randomisation (or from the pre-operative assessment visit for the monitoring study)
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1. Introduction

Background

In 2012, 76,448 primary hip replacements and 10,040 revision hip procedures were carried out in England and Wales. Infection is a serious complication of hip replacement and was the indication for 12% of all revision procedures. Blom and colleagues reported that deep infections occurred in approximately 1% of patients following hip replacement at a single NHS hospital in England [1].

Prosthetic joint infection (PJI) within 2 years of total joint replacement (TJR) is mainly surgically acquired [2], and is associated with joint pain and restricted movement [3]. 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 aseptic joint failure including implant loosening and joint pain. If untreated, PJI can result in severe pain, frequent dislocation, disability and death [3].

Andersson and colleagues studied patient experiences of deep surgical site infection after different procedures [4]. In interviews with 14 patients (12 orthopaedic), the authors reported that acquiring a deep surgical site infection was "an event that inflicted deep suffering and changed the physical, emotional, social and economic aspects of life in extremely negative ways." Cahill and colleagues compared outcomes in patients with uncomplicated recovery from TJR and those with PJI [5]. Disease specific measures of pain, stiffness and function were unfavourable in patients with PJI as were quality of life including mental health and social functioning. The ability to perform activities of daily living was reduced and satisfaction was low. Even in patients successfully treated, quality of life was worse than in patients with uncomplicated TJR.

Current Treatment Options

Contemporary treatment options for hip PJI are: surgical removal of dead, damaged and infected tissue (debridement) with prosthesis retention and long-term antibiotic treatment; 1-stage revision; 2-stage revision; excision or amputation. Surgical debridement and retention is considered in early PJI with pathogens susceptible to antibiotics and in patients unfit for surgery. However this approach may require lifelong antibiotic treatment [6].

Excision of the hip joint (Girdlestone procedure) or amputation is limited to patients with poor bone stock or infections unresponsive to antibiotics [7]. Some patients may chose excision and associated functional limitations over further surgery.

Surgical revision for a PJI involves prosthesis removal, debridement, antibiotic treatment and
joint replacement. The prosthesis is replaced in the same operation (1-stage) or delayed for 3-12 months (2-stage). In a 2-stage revision a temporary “spacer” may be fitted, but the patient has no hip or knee joint until it is replaced in the second operation. In England and Wales in 2012, treatment was 1-stage (37%), 2-stage (58%) and excision (5%) [8].

The best treatment option is unclear. 2-stage revision has the potential for additional antimicrobial strategies [9], but patient mobility and quality of life are poor between stages [5]. Design and reliability of spacers used between stages has improved. However, in a study of 88 hip spacers, Jung and colleagues reported spacer dislocation in 17.5%, spacer fractures in 10.2%, and femoral fractures in 13.6% of patients [10].

Resource use in 1-stage revision is lower with no planned second operation and a typical total hospital stay in the lead centre for this study of 14-20 days compared with 19-30 days for 2-stage. Overall healthcare costs of 1-stage revision may be about 40% less than 2-stage [11].

Existing Knowledge

Gallo and colleagues reviewed longitudinal studies and calculated overall re-infection rates after 1- and 2-stage hip PJI revision of 9.2% and 7.4% respectively [12]. Wolf and colleagues also reported an increased re-infection rate after 1-stage (12.3%) compared with 2-stage revision (6.5%) of infected THR [13]. However, in the studies they classified as 2-stage, more patients died.

To compare outcomes of 1- and 2-stage revision of infected hip replacements we systematically reviewed studies that included populations representative of patients in routine clinical practice. Irrespective of surgical treatment used, the overall 2-year rate of re-infection was 10.1% (95% CI 8.2, 12.0). In 11 studies with 1225 patients with infected hip prostheses receiving exclusively 1-stage revision, the rate of reinfection at 2 years was 8.6% (95% CI 4.5, 13.9). After 2-stage revision exclusively in 28 studies with 1188 patients, the rate of re-infection at 2 years was 10.2% (95% CI 7.7, 12.9). We conclude that on the basis of a systematic review of published data, there is no difference in the re-infection rate between 1- and 2-stage surgery [14].

Although research has shown that quality of life is poor in patients with PJI [5], little is known about the impact of treatment for PJI on patients, or patients’ perspectives and preferences in regard to treatment. Studies identified in our review provided little information on patient preferences and what outcomes they felt were important. Also, little is known about the cost-effectiveness of the two surgical treatments in relation to the NHS and in a broader societal perspective.
Rationale for the trial

Currently, both 1- and 2-stage revisions are carried out for PJI. Surgeons from the six collaborating centres are in agreement that a majority of patients could be treated with either 1- or 2-stage revision and that there is no definitive evidence to recommend a specific strategy in terms of clinical or patient outcomes. This is consistent with the conclusions of our review ("randomised trials are needed to establish optimum management strategies") [14] and those of Wolf and colleagues ("This study should be considered hypothesis-generating for future randomized controlled trials in which, ideally, health end points will be considered in addition to the eradication of infection") [13].

Unlike previous studies on infection after joint replacement, we plan to use patient-centred outcome measures rather than re-infection rates. This is because patient and public involvement work in the development of this application, as well as previous research around outcomes after surgery [15, 16], show that patients are concerned about pain, function and wellbeing after surgery, rather than a single bio medically defined outcome. This is particularly relevant to PJI as treatment appears to be distressing and has a substantial impact on quality of life. Qualitative research will form an integral part of this trial, informing the design and development of trial processes such as recruitment and randomisation, and to facilitate the interpretation of the trial findings.

In summary, the results from this trial should benefit patients, clinicians and NHS managers by enabling the comparison of these two widely accepted surgical treatments for infected hip replacements, in terms of patient reported outcomes, adverse events and cost-effectiveness.
2. Hypothesis
There is no difference in the WOMAC score (Western Ontario and McMaster Universities Arthritis Index), a patient reported outcome measure, at 18-months post-randomisation, after 1-stage or 2-stage revision surgery for prosthetic hip joint infection.

3. Trial Design
A multicentre, two arm, parallel group, unblinded, randomised, superiority trial with 1:1 treatment allocation and embedded qualitative and monitoring studies.

Figure 1 shows the patient’s involvement throughout the trial, including the components described below.

Embedded Qualitative Research
During the trial we will conduct a qualitative interview study to identify patients’ experience of taking part in the trial and being treated for PJH. The interviews will focus on the acceptability of the interventions, patients’ experiences during the follow-up period, covering issues around mobility and return to function, complications, expectations and how they feel that their treatment could be improved, if at all. We will also interview surgeons participating in the trial to explore the acceptability of the trial recruitment and randomisation processes. Findings from these interviews will help to refine trial processes and inform an understanding of people’s experiences and perceptions of the interventions.

Further details of the qualitative study methods are given in section 10.1.

Discrete Choice Questionnaire (DCQ)
The DCQ will explore patients’ preferences for surgical revision after hip PJH. We will assess the trade-offs that patients are willing to make between patient centred and clinical outcomes. Further details on the DCQ methods are provided in section 11.

Monitoring Group
Collection of baseline and follow up information from all patients with prosthetic hip joint infection is important to assess the external validity of the randomised controlled trial. We will offer those patients who are eligible, but unwilling to take part in the randomised trial, an opportunity to be part of a monitoring group.

Further details on the monitoring group methods are given in section 12.
Figure 1 INFORM Trial Flowchart

Patients with Prosthetic Hip Joint Infection

- Approached (n=290)
  - Not recruited
    - Declined
    - Missed
  - Consented
    - Baseline Measures
      - Randomise (n=142)
        - 1-stage surgery (n=71)
          - Pilot study interviews (30 patients and 20 surgeons)
            - Outcome Measures + DCQ (n=128)
              - End of Study Interviews (40 patients)
              - Surgeon Online Survey (n=30)
        - 2-stage surgery (n=71)
          - Non randomised Monitoring Group (n=80)
            - Baseline Measures
              - 1- or 2-stage revision surgery
                - Outcome Measures + DCQ (n=70)
            - Interview about reasons for declining trial
4. Participants

Study Setting

The INFORM trial will take place at NHS orthopaedic hospitals in England and Wales.

Selected sites are high volume tertiary referral centres for infected joint replacements, or large NHS orthopaedic units. Participating surgeons at each centre have experience and expertise with both 1-stage and 2-stage revision treatment.

Recruitment and Consent

Orthopaedic surgeons from the participating centres will identify patients under their care who are eligible for the study and approach them about taking part. The surgeon will document in the medical records that the patient meets the eligibility criteria for the trial and agrees to be contacted about taking part. Patients will be provided a patient information sheet and given at least 24 hours to consider the information before the research nurse contacts them to arrange a meeting. At this meeting, the research nurse will give a full explanation of the study and patients will have the opportunity to ask the research nurse, and their orthopaedic surgeon, any questions. Patients who wish to participate in the study will be asked to provide written informed consent, which will be recorded on the study consent form and in the patient’s medical records. Participants will also be asked if they are willing to be contacted in the future about research relating to the trial (e.g. long-term follow-up), and this will be documented on the consent form.

Patients who do not wish to take part in the randomised trial, but who would otherwise be eligible, will be invited to consent to the monitoring group (see section 12).

Patients who decline the randomised trial will be asked if they are willing to be contacted by a member of the research team by telephone to explore the reasons for their decision. The researcher will note their reasons for non-participation on a form. The information from these brief interviews will provide crucial information needed to allow us to refine the recruitment process. We have successfully used this method previously in a feasibility trial, which generated important information needed to improve trial recruitment [17].
Figure 2 Recruitment and Consent Process

- **Patient Identified**
  - Surgeon assesses eligibility
  - Patient invited to take part (in person or letter sent from treating surgeon)
  - Information sheet provided

- **Consent**
  - Research nurse meets patient to discuss study
  - Patient offered meeting with their treating surgeon
  - Adequate time allowed for patient to consider participation
  - Consent obtained

- **Baseline Assessments**
  - Primary questionnaire (WOMAC)
  - Secondary Questionnaire
  - 20m walk-test

- **Randomise**
  - Max. 12 weeks prior to surgery
  - WOMAC score entered into randomisation system
  - Research nurse informs patient and surgeon of allocation
  - Patient sent resource use log

- **Pre-Op visit**
  - Surgeon explains the intervention to patient
  - Consent for surgery taken

- **Surgery**
  - Case report forms completed
Recruitment Period
Recruitment will run for 3.5 years, during which time surgeons will approach all their eligible patients at the participating centres.

Audio recording of recruitment interviews and peer-listening
To refine and optimise the recruitment and consent process, research nurses will audio-record their recruitment interviews with patients [18]. Before commencing the interviews, study nurses will ask patients for their written consent to audio-record the recruitment interview, for training and research purposes. This process will be in accordance with the site’s local NHS policy on making audio recordings of patients or in the absence of such a policy, by using the study specific ‘Consent form for audio-recording of research discussion’, developed in accordance with General Medical Council guidelines http://www.gmc-uk.org/guidance/ethical_guidance/making_audiovisual.asp (accessed 5th November 2014). The audio-recordings will be peer reviewed by nurses at different participating centres. Research nurses will be invited to attend several feedback and peer review meetings during the trial, facilitated by the coordinating centre. During these meetings, peer reviewed recordings will inform discussions about how to optimise the recruitment procedure. These discussions will be informed by formal reports from the qualitative research in the pilot phase of the trial, including findings from interviews with participants and health professionals. This process has been successful in optimising recruitment in previous randomized controlled trials conducted at this centre [19].

Eligibility Criteria
Patients will be eligible for the trial if they are deemed clinically suitable for either 1-stage or 2-stage revision surgery by their treating surgeon.

Inclusion Criteria
Participants may enter the study if ALL of the following apply;

- Aged 18 or above
- A clinical diagnosis of prosthetic hip joint infection
- Require revision surgery (either 1-stage or 2-stage procedure) for prosthetic hip joint infection in the opinion of the treating consultant orthopaedic surgeon(s)

Exclusion Criteria
Participants may not enter the study if ANY of the following apply;

- Unable or unwilling to undergo either 1-stage or 2-stage revision surgery
- Lack capacity to give written informed consent for research
**Sample Size**

The required sample size has been set at 128 participants; allowing for a 10% loss to follow-up at 18 months post-randomisation, a total of 142 patients will need to be recruited. To reach this target, we will need to identify 290 eligible patients. The recruitment rate observed in a hip surgical joint trial recently conducted in the coordinating centre was of 51% with an attrition rate of 13% [20].

A sample size of 128 patients will provide 80% power to test that one surgical approach is superior to the other approach 18-months post-randomisation by 10 points of WOMAC (Western Ontario and McMaster Universities Arthritis Index) global score, equivalent to a 0.5 standard deviation difference. The significance level for this superiority hypothesis is set at 5% (two-sided).

Although it is known that infection following TJR reduces patient satisfaction and seriously impairs functional health and quality of life [5], there is no published research on the likely difference in patient-reported outcomes between patients undergoing 1- and 2-stage revision for PJI. The standard deviations observed prior to 1- or 2-stage revision surgery for WOMAC global and sub-scores range between 18 and 25 [5, 21, 22].
5. Randomisation

Randomisation will be conducted by the Bristol Randomised Trials Collaboration (BRTC), a UK Clinical Research Collaboration registered Clinical Trials Unit hosted by the University of Bristol. Randomisation will be by secure remote third party, either via an internet-based application or by telephone.

Randomisation will be carried out as close to the time of surgery as possible, and no more than 12 weeks before surgery. This takes into account the standard procedures in each centre for arranging theatre schedules, ordering equipment and obtaining patient consent for the operation.

Allocation concealment will be ensured, by not releasing the treatment allocation, or the randomisation code, until the patient has been recruited into the trial, and all baseline measurements have been completed. Eligible participants who consent to the study will be registered on the central trial database, issued with a unique study identification number and have their baseline measures collected prior to the treatment allocation being generated, so ensuring judgments about eligibility are made without knowledge of what the next allocation will be (allocation concealment). Patients will then be randomly allocated in a 1:1 ratio to one of the treatment groups (1-stage or 2-stage revision surgery). Randomisation within blocks of varying size will be conducted separately for each hospital to guarantee balance between arms in each treatment centre. Block sizes will not be disclosed, to ensure concealment.

Due to the nature of the intervention neither participants nor staff can be blinded to allocation. The primary outcome will be collected at 18-months post-randomisation by an assessor blinded to allocation.
6. Interventions

All surgeons that participate in the trial will be experienced in the treatment of prosthetic hip joint infection. The overwhelming majority of revision procedures of the hip performed for diagnoses other than infection are performed as 1-stage procedures; hence all surgeons are familiar with this approach in their day-to-day clinical practice. All surgeons that will participate in the trial perform 2-stage revision procedures for infection as part of their routine clinical practice and work in high volume primary and revision hip arthroplasty centres.

The design of the trial is pragmatic in nature with the diagnosis of infection being determined by the treating surgeon or multidisciplinary team in the unit treating the patient. Treatment decisions will be made according to local procedures and protocols and at the discretion of the treating clinical team including but not limited to:

- Investigations prior to surgery including haematology, biochemistry, microbiological and radiological testing
- The surgical approach employed
- The surgical environment
- Use of locally delivered antibiotics, static or articulating spacers between stages in 2-stage surgery
- Choice of implants and fixation at the time of definitive re-implantation
- Pre-, peri- and post-operative antibiotic regimes will be determined by local treatment resources and by liaison between the treating surgical and microbiology teams
- Peri- and post-operative analgesia regimes

Standard Protocol for Both Interventions

At the time of surgical intervention(s), all cases will have 5 separate samples collected from different sites with clean instruments to allow an adequate number and quality of samples to be available for microbiological testing.

Pre-operative

- Aspiration of fluid from the joint will be sent for microscopy, culture and sensitivity testing (microbiological testing). Note; this will not be required in all cases e.g. a sinus communicating with the prosthesis.
- Pre-operative antibiotic regimes (type, duration, route and dose) will be determined by the treating surgeon in liaison with the local microbiology team where required.
Intra-operative

- The surgical approach and techniques employed will be at the discretion of the treating surgeon
- Tissue and/or fluid samples will be collected from 5 surgical sites and sent for microbiological testing (microscopy, culture and sensitivity (MC&S))
- All patients will undergo debridement and irrigation of the surgical site at each surgical intervention

Post-operative

- The occurrence of reinfection will be determined by the presenting clinical history and signs as elicited by the treating clinical team consistent with the preoperative diagnosis of infection
- Response to treatment will be monitored by blood tests (e.g. CRP) as clinically indicated
- Post-operative antibiotic regimes (type, duration, route and dose) will be determined by the treating surgeon in liaison with the local microbiology team where required
- Patients will remain an inpatient until it is determined that the patient is appropriate for discharge by their treating surgeon
- Outpatient follow-up (frequency) and clinicians present (consultant surgeon, microbiologist) at outpatient review will be determined by local resources and clinical need.
- The weight-bearing status and rehabilitation limitations appropriate for the patient will be determined by the treating surgeon at the time of operative intervention pending review of post-operative radiographs as required.

Variations between Interventions

2-stage Revision

- Antibiotics between stages (e.g. duration, route) will be prescribed according to local guidelines at each centre.
- The use of delivery of local antibiotics and the use of a static or articulating spacer will be determined by the surgeon depending upon intra-operative findings at the time of surgical intervention.

Treatment Modifications and Discontinuation

The assigned treatment may need to be modified or discontinued by trial investigators due to patient improvement or deterioration or withdrawal of participant consent. Regardless of the reason to modify or discontinue treatment, study participants should remain in the trial whenever possible to enable follow-up data collection.
Protocol deviations and participant withdrawals

When identified, protocol deviations and participant withdrawals will be detailed on the appropriate report forms and stored in the CRF. A copy will be put in the participants medical records and also sent to the INFORM co-ordinating centre for review by the Chief Investigator. Quarterly reports will be generated for the DMC.
7. Outcome Measures

Primary Outcome Measure

Patient reported outcomes at 18–months after randomisation, as measured by WOMAC score of hip pain, function and stiffness.

Previous work has shown that functional recovery starts to plateau at around 12 months after revision surgery [23]. As the second intervention of patients assigned to 2-stage treatment is usually happening within 3 to 6 months after their first surgery (12 months maximum), assessing the primary outcome at 18 months is clinically relevant. Performing this assessment later would increase the risk of bias induced by loss to-follow-up.

Secondary Outcome Measures

Hip complications during trial period, measured by:

- Hospital readmissions (reason for admission and length of stay)

Post-operative pain, measured by:

- Brief Pain Inventory

Hip Function, measured by:

- Patient reported hip function (Oxford Hip Score)
- Performance test (20m timed walk)

Hip Re-infection / Continued Infection, measured by:

- Hip Infection Status. To be determined by the treating surgeon from patient history, clinical examination and investigations

It is not part of this protocol or current study to follow-up patients beyond 18 months from randomisation; approximately the date of their first operation. However, in order to study differences in re-infection, a longer follow-up period is needed. To make this possible, we will ask patients if they are willing to be contacted in the future about research relating to their hip.

Health and Quality of Life, measured by:

- General Health (EQ-5D-5L)
- Depression and Anxiety (HADS)
- Quality of life (HOOS QoL subscale)
- Cost-effectiveness of interventions, measured by:
  - Resource Use
Measurement of Outcomes

The WOMAC score and complications data will be collected by phone, post or in person by a research nurse. The primary outcome measure (18 month post-randomisation) will be collected by an assessor blinded to allocation.

Secondary outcomes will be collected by the research nurse in person at pre-operative assessment and by postal questionnaire.

Patients will also be invited to complete a walk-test in clinic. They will be timed and supervised by a research nurse as they walked a 20-metre straight distance on level ground at their normal, comfortable speed.

The research nurse will complete a case report form at the time of revision operation(s), providing details of the surgical procedures, complications and resource use in hospital. The research nurse will also collect information on subsequent inpatient stays and outpatient visits.

Resource use will also be collected using resource use questionnaires administered at 6, 12 and 18 months post-randomisation.

To maximise the response rate, patients will be reminded by phone to complete and return their questionnaires by the local research nurse at each site, a maximum of two times for each mailing. The first reminder will be just prior to the questionnaires being sent, and whilst collecting the WOMAC and complications data. The second reminder will only occur if the questionnaire has not been received back at the co-ordinating centre two weeks after posting it. The questionnaires will be re-sent if the patient reports not having received it.

The components and timing of follow-up measures are shown in Table 1

End of study definition

The end date of the trial will be 18 months following randomisation of the last patient or if the trial steering committee feels that interim data analysis justifies early cessation.
Table 1 - Measurement of Outcomes: Components and Timing

<table>
<thead>
<tr>
<th>Outcome Data</th>
<th>Time Post-Randomisation</th>
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<tbody>
<tr>
<td></td>
<td>Base-line</td>
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<tr>
<td>Primary Questionnaire</td>
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<tr>
<td>Secondary Questionnaire</td>
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<tr>
<td>Resource Use Questionnaire</td>
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<td>20m timed walk test</td>
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<tr>
<td>Discrete Choice Questionnaire</td>
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<tr>
<td>Case Report Form</td>
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</table>

* Measure repeated for 2nd of 2-stage surgery (variable time-point)

- Hospital / Home Visit
- Telephone Questionnaire
- Postal Questionnaire
- Medical / Theatre Records
8. Data and Statistics

Data Collection
The questionnaires or CRF will be completed by the patients or the research nurse and sent to the co-ordinating centre which will input the data in a secure electronic database.

Primary Questionnaire
- WOMAC (Western Ontario and McMaster Universities Arthritis Index pain, function, stiffness scales) [5, 24, 25].
- Complications (not included in baseline questionnaire).
  - Dislocation, Deep vein thrombosis, Pulmonary Embolism, Nerve Damage.
  - Hospital re-admissions (all reasons relating to hip).
- EQ-5D-5L (at 3 month assessment).
- Socio-demographic status (at baseline only).

Secondary Questionnaire
- BPI (Brief Pain Inventory) [26].
- OHS (Oxford Hip Score) [27].
- HADS (Hospital Anxiety and Depression Scale) [28].
- EQ-5D-5L (Euroqol health questionnaire) [29].
- HOOS QoL (Hip dysfunction and osteoarthritis outcome score – Quality of life) [30].
- FCI (Functional Co-morbidity Index) [31].

Resource Use Questionnaire
A resource use questionnaire will be posted to participants with the secondary questionnaire. It will include information on; non-treating hospital resource use, community based health service use, social service use, travel, time off work, usual activities and informal care in relation to the patient’s prosthetic joint infection.

Resource Use Diaries
At the pre-operative assessment clinic, prior to their first surgery, patients will be given a resource use diary in which they will be asked to record prospectively their resource use. It will not be a data end point, but to be used by patients as an aide memoire to help them to complete the follow-up questionnaires.
Case Report Forms (CRF)
CRFs will be completed by the research nurse from the participant’s medical records.

Pre-Operative
- Contact info (Address, Phone No’s, Email)
- Age, Sex, BMI (Body Mass Index)
- Diagnosis of infection (date, surgeon, relevant clinical signs/markers)
- Details of previous surgery to hip pertaining to study
- Details of planned revision surgery

Intra-Operative
- Date of admission and date of operation
- Surgery details: Type of procedure; surgical approach; implants removed, retained or implanted (including spacers); type of fixation; presence or absence of local antibiotic delivery with type and dose of antibiotic
- Systemic antibiotics administered in theatre
- Microbiology samples ( Cultures and Sensitivities)
- ASA grade (Anaesthetic Risk Score)

Post-Operative
- Date and place of discharge
- Antibiotics administered on ward and prescribed to take home

Complications and adverse events
- All events post-randomisation, relating to the hip pertaining to the study

Resource Use
- All hospital inpatient episodes and outpatient visits post-randomisation, due to hip pertaining to study

Hip Infection Status
Evidence of continuing hip infection or reinfection, including;
- Responsible organisms and antibiotic use
- Diagnostic signs, symptoms and markers
- Further surgery for infection (e.g. debridement, revision)
- Time to further surgery

Performance test
- Time taken to complete a 20 metre walk-test (carried out according to a standard procedure and recorded on a CRF)
Data Storage and Security
Data collection forms will be anonymised by the study site and will be identified by the participant’s unique study ID. A list of participant’s names and addresses, with corresponding study ID will be stored separately from the study data and kept securely at the co-ordinating centre.

Data collection forms will be scanned and sent by secure email to the co-ordinating centre. Original data collection forms will be retained by the study site, stored securely and be available for audit on request of the Sponsor.

Procedures for data entry, promoting data quality and data queries will be described in a separate standard operating procedure.

Participants’ contact information will be retained by the University of Bristol for 20 years after the study has been completed to allow for an adequate follow-up period. This is in accordance with Medical Research Council guidelines on archiving research records in clinical studies:
(http://www.dt-toolkit.ac.uk/researchscenarios/archiving.cfm accessed on 2nd September 2019). Data procedures will be in keeping with the stipulations in the Data Protection Act 2000.

Statistical Analysis
Sample description and participation
Analysis and presentation of data will be in accordance with the CONSORT guidelines for reporting randomised trials.

Summary statistics describing the conduct of the trial will be presented, including the number and percentage of potentially eligible, confirmed, randomised and completing outcome measurements patients.

The baseline characteristics and primary outcomes will be described by treatment group. The secondary outcomes will be also be presented by treatment group and where required by assessment point.

Means with standard deviation or median with inter-quartile range will be reported for continuous variable, frequency and proportions for categorical or binary variables, as appropriate.
Primary analysis

The primary outcome is the continuous WOMAC global score collected at 18 months post-randomisation. Published studies have shown that there is less overall improvement in patient-reported outcome scores in revision hip arthroplasty, than for primary hip arthroplasty [32]. There is also a plateau effect in WOMAC scores around 12 months in primary and revision groups but patients who undergo revision arthroplasty maintain lower scores [24]. In revision for infection, outcomes are worse than for other types of revision [33]. Therefore, we expect our study population to have lower baseline score and a slower rate of improvement than in other revision arthroplasty. This should result in more heterogeneity in score distribution and a low ceiling effect at 18 months post-randomisation. Due consideration will be put on the residuals of the following models. Appropriate linear transformation of the WOMAC score will be considered or other link function in the GLLM will be considered if required.

The primary analysis will be based on the intention-to-treat principle, analysing participants in the groups to which they were randomised.

Please refer to the full Statistical Analysis Plan for details.
Cost-effectiveness Analysis

We will conduct an intention to treat cost-effectiveness analysis from a societal perspective with costs to the NHS reported and analysed separately. All costs will be reported in 2018/19 prices, and discounting will be applied as appropriate.

Health service resource use will be valued using hospital finance department and routine UK data. Social service, patient and informal carer resource use will be valued using self-reported data.

The net monetary benefit statistic, using the difference in costs and the difference in QALYs between groups, will be calculated for different values of societal willingness to pay for a QALY. This will be the primary economic analysis. We will adjust for the randomization minimisation variables and baseline values, and any covariate imbalances using multivariable linear regression. Multilevel modelling will be used to examine centre effects. The secondary economic analysis will examine the difference in costs with the differences in the WOMAC score. If no arm is dominant, i.e. does not have statistically significant improved WOMAC score and lower costs, then an incremental cost-effectiveness ratio will be estimated and a cost-effectiveness acceptability curves will be derived using bootstrapping techniques. These will show the probability of the intervention being cost-effective at a range of ‘willingness to pay’ thresholds.

Sensitivity analysis will account for uncertainty and imprecision in measurements including multiple imputation models for missing values.

Please refer to the Health Economics Analysis Plan for further details.
9. Adverse Events

Definitions

Adverse Event (AE) is defined as any untoward medical occurrence in a trial participant, not necessarily having a causal relationship.

Serious Adverse Event (SAE) is defined as any untoward and unexpected medical occurrence or effect that:

- Results in death
- Is life-threatening – refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe
- Requires hospitalisation, or prolongation of existing inpatients’ hospitalisation
- Results in persistent or significant disability or incapacity
- Is otherwise considered medically significant by the investigator

Medical judgement should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

Unrelated Adverse Events

Adverse events unrelated to the trial procedures are:

- Length of hospital stay after hip revision surgery prolonged by up to 21 days, due to factors unrelated to the surgery.

Expected Adverse Events

Possible (expected) adverse events associated with surgery are:

- Scar, bleeding, infection, DVT, PE, persistent pain, stiffness, nerve injury, fracture, leg length discrepancy, dislocation, wear and loosening.
Reporting Procedures

All AEs will be reported on the adverse event form (even if originally noted on the CRF or questionnaire). If, in the opinion of the local investigator, the event is serious, it must be faxed to the trial co-ordinating centre. The Chief Investigator (CI), or trial manager, will notify the sponsor within 24 hours of receiving the SAE.

The CI (or trial manager) will report any related and unexpected SAEs to the main Research Ethics Committee and the DMC within 15 days of the CI becoming aware of the event.

Local investigators should report any SAEs as required by their Local Research Ethics Committee, Sponsor and/or Research & Development Office.

Any questions concerning adverse event reporting should be directed to the Chief Investigator in the first instance.

Contact details for reporting SAEs:

Please send SAE forms to:
INFORM trial office Musculoskeletal Research Unit, Level 1 Learning and Research Southmead Hospital, Bristol BS1 5NB
Fax: 01174147924
Tel: 01174147866
10. Pilot Study
An internal pilot study will take place during the first 6 months of the trial to identify whether adequate recruitment rates are feasible and to enable refinement of recruitment processes based on qualitative and peer-listening approaches. By the end of the pilot phase it is anticipated that all sites will have recruited patients and some patients will have completed the 3-month follow-up assessment. The trial management group will continually monitor recruitment rates, to assess if these are consistent with those required for the main trial. Sites that are under-recruiting sites will be investigated and optimization strategies implemented. At 6 months (with an estimated 30 patients randomized), the questionnaires and CRFs will be reviewed and any improvements and changes needed will be submitted for ethical approval. All patients recruited into the pilot study will continue with the follow-up schedule described in the protocol (see Table 1 - Measurement of Outcomes: Components and Timing) and will count towards the main sample.

11. Embedded Qualitative Interviews and Survey
During the trial we will conduct a qualitative study designed to explore surgeons’ and patients’ experiences of participation in the trial, and patient experiences of the intervention and recovery after PJIL. These will be in-depth telephone and face-to-face interviews. An online survey will be conducted with surgeons at the end of the trial.

Patient Interviews
Qualitative interviews with patients will be carried out at two different time points.

At time point 1: During the pilot phase of the trial, telephone interviews with patients will focus on patients’ understanding and experience of the recruitment and randomisation process, and their acceptance of participation within the trial. This will inform refinements to trial processes to optimise its acceptability to patients. Also, patients may wish to talk about their experiences of the revision surgery and after care, and this will help to inform our understanding of treatment and care. Ideally patients will be interviewed by telephone after they have been discharged from hospital after their operation. The data will provide a more accurate depiction of patients’ experiences the closer it is to the treatment event [34]. The semi-structured telephone interviews will use a topic guide developed by the study team in collaboration with patients in patient and public involvement activity.

All participants recruited to the study during the pilot phase will be asked during the trial
consent process if they are willing to be interviewed about their experiences of taking part in the study and their treatment. Those who agree to be interviewed, will then be given an additional information sheet about the qualitative interview study (to avoid over-burdening participants) and told that a researcher will telephone them approximately 2 weeks after they are discharged from hospital, to arrange a convenient time for interview. To enable all to take part, those who request face-to-face interview rather than a telephone interview will be interviewed in person at a place convenient to them (either their home or hospital). Potential participants will be asked to provide their verbal informed consent for the interview if the interview is conducted by telephone, or their written consent if the interview is conducted face-to-face. Depending on trial recruitment rates, we expect to interview up to 30 patients, which will provide sufficient depth and breadth to inform refinements to trial processes and an understanding of patient experiences of treatment and care. If we cannot interview up to 30 within the pilot phase we will continue to interview beyond the pilot phase or until data saturation is reached.

At time-point 2: We will invite those who participated in the interviews at time point 1 to interview again at the end of the study (approximately 18 months later). However, we envisage that not all will be able or wish to take part, and we need ensure that a range of outcomes are included at this point in time. Therefore, we may enhance the sample from time point 1 to ensure maximum variation at time point 2 with a sample of up to 40 patients at this point. The sample will include all of those who took part in qualitative interviews at time point 1 who are willing and able to take part, as well as additional patients identified through the trial and who have indicated that they are willing to be contacted about taking part in an interview. From those who agree we will identify a sample of potential participants including those in each intervention group (1- and 2-stage), men and women with a variety of outcomes. This purposive sampling strategy will provide a range of experiences and opinions [35]. The sample size of up to 40 patients has been identified by the study team as likely to achieve saturation, such that no new themes are emerging by the end of analysis [36, 37].

Patients who agree to be contacted about taking part in interviews when they consented to take part in the trial will be sent an information pack about the end of study interview, which will include a letter of invitation and an information booklet describing the purpose and aims of the interview, a reply slip and a FREEPOST addressed envelope. The information booklet will also state that they should return the reply slip in the envelope indicating whether or not they are interested in taking part and that if they find it difficult to get to a post box because of their condition a member of the research team will contact them by telephone 7 days after
the information pack is posted out to them to check that the information pack has arrived and to discuss the research with them. This will provide an opportunity for patients to express an interest in participating in the interviews at which point the researcher will arrange an interview date. Participants will be asked to provide their written informed consent for the interview. If a family member, or friend is also present at the interview and wishes to contribute we will ensure that they have read the information booklet and if they wish to take part we will ask them to sign a separate consent form.

The semi-structured interviews at time point 2 will be conducted by the qualitative researcher, using a topic guide that has been developed on the basis of previous qualitative research (INFORM work package 3 and the time point 1 interviews) and patient and public involvement. Interviews will focus on patients’ experiences of taking part in the trial, undergoing treatment for PJL, the acceptability of the interventions, and their experiences during recovery and the follow up period, as well as covering issues around mobility, return to function, complications, expectations and how they feel that their treatment could be improved if at all.

*Surgeon Interviews*

Alongside interviews with patient participants, we will conduct telephone interviews with up to 20 surgeons during the pilot phase to explore their experience and acceptance of the randomisation process, their understanding of equipoise, and their views on information about the trial and treatment interventions. Surgeons will be sent an information pack which will include a letter of invitation, an information booklet describing the purpose and aims of the interview, a reply slip, a consent form and a FREEPOST addressed envelope. The information booklet will state that they should complete the reply slip and if they wish to take part the consent form, in the envelope provided. Once an interview is arranged, the researcher will countersign the consent form and forward a copy to the surgeon before the interview. Data from these interviews will help to inform the recruitment process during the pilot phase and will help to identify any areas that can be improved.

**Reporting of qualitative findings during pilot phase**

Findings from the patient and surgeon interviews will be reported at regular intervals to the Programme Steering Committee during the pilot phase, ensuring that any issues relating to information about the trial, the conduct of the recruitment and randomisation process, and the interventions are reported in a timely fashion to facilitate remedial action. Reports will also be provided to the peer-listening groups that will be reflecting on recruitment interviews. These data will inform the ongoing recruitment process during the pilot phase and will help to identify any weaknesses or unforeseen ethical issues and areas for improvement in the recruitment process.
Analysis of Patient and Surgeon Interview Data

With participants’ consent the interviews will be audio-recorded, transcribed and anonymised. Transcripts will be imported into software package QSR NVivo and data will be analysed using a combination of 3 approaches:

1. The Framework Method provides a systematic and flexible approach to analysing large amounts of qualitative data and can greatly facilitate constant comparative techniques through the review of data and facilitate the management of large data sets [38].

2. Constant Comparison: Transcripts will be coded, using in-vivo codes as much as possible and the codes will be grouped, using inductive methods, into categories [39]. The proposed analytical approach provides a flexible and useful research tool and involves identifying salient themes and patterns across the data set. The researcher, Dr Andrew Moore will code the transcripts with 20% of these double-coded by Dr Rachael Gooberman-Hill until a working analytical framework is developed. Data from patients in the 1-and 2-stage groups will be analysed separately. This will allow for any differences in experience between the groups to become apparent and will enable the team to identify when saturation has been achieved. The data sets will then be compared and contrasted to enhance insight into the experience of treatment and recovery for both groups.
   NB: Data from the Surgeons’ interviews will only be analysed using the Framework and constant comparative methods.

3. A longitudinal approach: Where patient participants have taken part in both interviews a longitudinal approach to analysis will be used. A focused within-case and cross-case longitudinal analysis will be conducted using descriptive and interpretive questions [40] to determine within the data what happened during the treatment and recovery period, any processes of change, and the key time points at which these changes occurred, and the key influences on these changes. This will help to build a picture of individuals’ recovery trajectories and the key influences on change in health and well-being, and also the differences and reasons for any changes in people’s accounts between the post-intervention and follow up interviews [41].
Surgeon Online Survey

After recruitment to the trial has finished we will conduct a survey designed to explore surgeons’ experiences of participation in the trial, and in particular, whether participation in the trial has changed their practice. This will be an online survey, using the Bristol Online Survey (BOS) tool.

All surgeons who have recruited patients to the INFORM trial will be invited to complete an online survey after recruitment to the trial has ended. The online survey will focus on surgeons’ experience of participating in the trial and will explore whether they feel their participation has changed their practice, including their decision-making about single or two-stage revision surgery from prosthetic hip joint infection. This will help to inform our understanding of how participation in clinical trials might affect clinical practice. The online survey will be developed by the study team using findings from the previous surgeon interviews.

Surgeons will be sent an invitation pack by email, which will include a letter of invitation with information describing the purpose and aims of the survey, and a URL link to the survey itself. In the invitation letter and at the beginning of the survey, surgeons will be informed that by completing the survey they are giving their consent to participate and for their anonymised data to be published in peer reviewed journals. The introductory statement will also include information about the purpose of the survey and data protection. We expect to contact approximately 30 surgeons, who have all recruited to the INFORM trial. Non-responding participants will be contacted 2 weeks after initial invitation and will be supplied with a new information pack if requested.

Analysis of Data: Surgeon Online Survey
Data will be analysed using descriptive content analysis, identifying and describing items of interest within the responses and producing a descriptive summary of the data including a description of the variability in responses and any common themes and patterns that are identified.

Outputs from Embedded Qualitative Study and Surgeon Survey
The qualitative and survey data will provide context to and facilitate the interpretation of the findings of the main trial whilst providing evidence about the acceptability of revision methods and highlight issues around recovery and the follow-up period. The longitudinal method will allow us to identify processes of change within individuals’ recovery trajectories.
and any influences on these changes in health and well-being and help us to identify any facilitators and barriers to recovery. While previous qualitative work has provided some indication of how traumatic infection and revision treatment can be for patients, the data has been collected long after the event itself and may not be as representative of the challenges patients face at the time. Interviewing soon after the event and again at the point of recovery will help to inform a more nuanced understanding of the impact of infection and these two treatment interventions.

12. **Discrete Choice Questionnaire (DCQ)**

This component of the study will explore patients’ preferences for the attributes associated with surgical revision after hip PJL. We will assess the trade-offs that patients are willing to make between the features of surgical options, including both patient centred and clinical characteristics.

The DCQ technique works on the premise that any ‘product’, in this case a surgical regime, can be described by its characteristics and the extent to which an individual values the ‘product’ is dependent on the level of these attributes. By offering participants a choice of scenarios made up of a combination of the different attributes and levels of the ‘product’ on offer, the relative value of each attribute can be determined.

The attributes and levels that emerge from the qualitative interviews being conducted as part of the INFORM programme, will be used to design a DCQ that will be provided to two samples of patients [42].

There is currently no recognised mechanism for defining DCQ sample sizes as it requires prior knowledge on the variability in preferences in an area where typically none is available. However, previous DCQ studies have satisfactory precision in their coefficients with sample sizes above 50. Larger samples will enable more insights to be drawn between subgroups (e.g. patients <70 years old and those >70).

Two samples of patients will be selected in order to provide a comparison of preferences for those with different surgical experiences, and both will receive the same DCQ. Sample 1 will comprise approximately 70 non-randomised (monitoring group) participants. This sample will be matched as far as possible to patients in the randomised trial according to key variables such as age and gender. Sample 2 will comprise approximately 70 randomised trial participants. The DCQ will be sent to selected participants with the 18 month outcomes questionnaires. A response rate of 40% (after one reminder) will be assumed (compared to 20% commonly assumed for general population studies), given that the subject will likely be
of inherent interest to respondents. DCQs will be sent to the INFORM trial co-ordinating centre for data entry and anonymisation. Data will be analysed by Dr Fran Carroll at the University of Bristol.

Choice data will be analysed using conditional logistic regression to estimate the relative value of the different attributes of the surgical intervention. Scale-adjusted latent class analyses [43] may also be used to investigate any differences in preference structure across the samples. Any differences in preferences and/or scale will be related to socio-demographic, health and other observed characteristics of respondents. Archetypal analysis [44] will allow us to identify the patient who is most concerned about each particular attribute, which may allow us to characterise different “types” of patient based on their preferences.

13. Monitoring Group

Rationale for follow up of all patients with prosthetic hip joint infection

Comparison of patients in the randomised controlled trial and those participating in the monitoring group will allow us to assess whether randomised patients are representative of the general population of patients with prosthetic hip joint infection. This will advise on how generalisable the results of the randomised trial are to the wider population of patients with prosthetic hip joint infection. Generalisability will relate to baseline characteristics, control of infection, other adverse events and patient outcomes.

Further to providing support to the randomised trial in terms of external validity, follow up of all patients with prosthetic hip joint infection will represent the largest and most detailed cohort study of prosthetic hip joint infection ever conducted.

The monitoring group will undergo treatment as per usual clinical practice, and then will be asked to complete questionnaires including the discrete choice questionnaire (see section 11).

Data Collection

Data will be collected at pre-operative assessment (baseline) and at 6, 12 and 18 months after baseline. Patients in the monitoring group will not be asked to attend hospital for research visits.

The following information will be collected from patients by a research nurse, via telephone (or at home/hospital visit if patients prefer): Primary questionnaire (section 8.1.1)

The following information will be collected from each patient’s medical notes by a research nurse: CRFs, excluding resource use and performance test (section 8.1.5)

The Discrete Choice Questionnaire will be posted to patients at 18 months.
Analysis Plan

The external validity of the trial results will be assessed by comparing the baseline patient characteristics and WOMAC scores of the trial sample to those of the observation sample. Percentage, mean or median values with their respective standard deviation or interquartile range will be reported by sample source (trial or monitoring) and compared using appropriate parametric or non-parametric tests. WOMAC scores at 18 months will then be compared between the two samples and by surgical treatment (1 or 2 stages surgery) using an appropriate generalised linear model. Differences in patterns of recovery by sample source and surgical treatment will also be investigated using the repeated measurements of WOMAC score (preoperative, 6, 12 and 18 months) and generalised linear mixed models. If appropriate, the analyses will then be adjusted for any relevant baseline characteristics. The analyses for the discrete choice questionnaire are described in section 11.

Finally, rates of adverse events including the rate of re-infection will be investigated by pooling the two samples together and then comparing the figures across samples and surgical treatments. Generalised linear model and survival analysis will be considered. Analyses will be used to provide a report about the external validity of the randomised trial, a report about outcome after PJI for patients and patient preference as examined through the discrete choice questionnaire.

14. Trial Management

Public and Patient Involvement

In the development of the programme we collaborated with patient-partners and the leading UK charity supporting people with arthritis: Arthritis Care.

Collaboration with patient-partners took place through meetings with our dedicated patient involvement group at the Musculoskeletal Research Unit, University of Bristol (‘The Patient Experience Partnership in Research: PEP-R’ [45]. PEP-R currently comprises 8 people who have musculoskeletal conditions, most of whom have had joint replacement. PEP-R members have expressed ongoing commitment to the INFORM Programme and in September 2014 discussed the patient recruitment literature. We provide a structured system of support and training to patient-partners involved in research.

To complement PEP-R's activities in more specialised dialogue between researchers and patients, an additional patient forum for the Programme was established in December 2013, comprising four to six patients with experience of infection following joint replacement. This will be the INFORM forum, meeting every two months. Relatives and significant others of group members will also been invited to attend selected meetings. By using the group’s
existing expertise, and providing support and training, the programme will benefit from their knowledge of personal experiences.

**Trial Management Team (TMG)**

The trial office is at the Musculoskeletal Research Unit, University of Bristol. It is responsible for all data collection (such as mailing questionnaires), data processing and analysis. It is responsible for communicating with the INFORM study sites about specific trial issues and for producing newsletters for participants and collaborators about progress.

**Programme Steering Committee (PSC)**

The role of the PSC is to provide overall supervision and monitor the progress of all aspects of the programme including the trial. The PSC will ensure that the trial is being conducted in accordance with the protocol, relevant regulations and to principles of GCP. The specific tasks of the PSC will be to approve the protocol and any necessary changes based on considerations of feasibility and practicality; receive and act on reports from the Data Monitoring Committee (DMC); resolve any issues brought to it by the TMG; approve reports and papers for publication.

The PSC consists of four independent members (including the chair) and the CI (or a deputy). Other members of the TMG or members of other professional bodies may attend at the invitation of the chair. Representatives from the funder and the sponsor will be invited to attend all meetings and receive minutes. The PSC will comprise of:

- Independent Chair & Statistician: Rod Taylor
- Independent Orthopaedic Surgeon: Martyn Porter
- Independent Qualitative Researcher: Ali Heawood
- Layperson: Julie Chappell
- Chief Investigator: Ashley Blom

**Data Monitoring Committee (DMC)**

A separate independent data monitoring committee will be convened. It is anticipated the members will meet once to agree terms of reference and on at least three further occasions to monitor accumulating data and oversee trial recruitment, retention and safety issues. The content and frequency of the interim analyses will be decided by the chair of the DMC. In light of these analyses the DMC will advise the PSC, which can decide whether or not to modify or terminate the trial.
15. **Regulatory Issues**

**Research Ethics Approval**

The Chief Investigator has obtained approval from the NRES Committee South West - Frenchay Research Ethics Committee. The trial must be submitted for Site Specific Assessment (SSA) at each participating NHS Trust. The Chief Investigator will require a copy of the Trust R&D approval letter before accepting participants into the trial. The trial will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

**Consent**

Consent to enter the trial must be sought from each participant only after a full explanation has been given, an information leaflet offered and time allowed for consideration. Signed participant consent should be obtained. The right of the participant to refuse to participate without giving reasons must be respected. After the participant has entered the trial the clinician remains free to give alternative treatment to that specified in the protocol at any stage if he/she feels it is in the participant’s best interest, but the reasons for doing so should be recorded. In these cases the participants remain within the trial for the purposes of follow-up and data analysis. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment.

**Confidentiality**

The Chief Investigator will preserve the confidentiality of participants taking part in the trial and is registered under the Data Protection Act.

**Indemnity**

North Bristol NHS Trust holds standard NHS Hospital Indemnity and insurance cover with NHS Litigation Authority for NHS Trusts in England, which apply to this trial. The Patient Information Sheet provides a statement regarding indemnity for negligent harm.

**Monitoring and Audit**

The Principle Investigator (PI) will allow monitors, persons responsible for the audit, representatives of the Ethics Committee and of the Regulatory Authorities to have direct access to source data / documents. Study monitoring will be undertaken by North Bristol NHS Trust under their remit as sponsor.
Access to Source Data / Documents at remote sites

The PI will allow the monitor and/or the Sponsor to:

- Inspect the site, the facilities and the material used for the study
- Meet all members of his/her team involved in the study
- Consult all of the documents relevant to the study
- Check that the CRFs have been filled out correctly
- Directly access source documents for comparison of data therein with the data in the CRFs
- Verify that the study is carried out in compliance with the protocol and local regulatory requirements
- Carry out study monitoring at regular intervals, depending on the recruitment rate, and arranged between the PI and monitor

All information dealt with during these visits will be treated as strictly confidential.
**Publication Policy**

All co-applicants (and where appropriate collaborators) will take an active part in the preparing and reviewing of all manuscripts and reports generated during or as a result of this study. In line with contractual agreements with NIHR the authors will inform NIHR of any publications at least 28 days prior to publication.

**Dissemination Policy**

In addition to provision of annual and final reports, as well as presentations at scientific meetings and publication of findings in scientific literature, all participants in the trial will be sent a summary of the final results of the trial which will contain a reference to the full paper. A copy of any related journal articles will also be available on request from the Sponsor. Furthermore, depending on the final findings of the trial, the Investigators may also seek further dissemination funding from other sources, to maximize the level of dissemination to both potential service users and professionals.
## 16. Study Timelines

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