Hip Implant Prosthesis Programme for the Younger total hip replacement patient (HIPPY)

Trial protocol

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Abbreviations

AE	Adverse event
AR	Adverse reaction
BMJ	British Medical Journal
BTC	Bristol Trials Centre
CI	Chief Investigator
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case report form
DMC	Data monitoring and safety committee
GCP	Good Clinical Practice
GP	General Practitioner
HES	Hospital Episode Statistics
HEAP	Health Economic Analysis Plan
HIPS	Hip Implant Prosthesis Study
HRA	Health Research Authority
HRG	Healthcare Resource Group
HRQoL	Health-Related Quality of Life
HTA	Health Technology Assessment
MHRA	Medicines and Healthcare products Regulatory Agency
MRC	Medical Research Council
NBT	North Bristol NHS Trust
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NJR	National Joint Registry
ONS	Office of National Statistics
PI	Principal Investigator
PIL	Patient information leaflet
PP	Per protocol
PPIE	Patient and Public Involvement and Engagement
PROM	Patient Reported Outcome Measure
PSC	Programme Steering Committee
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
REC	Research ethics committee
SAE	Serious adverse event
SAP	Statistical analysis plan
SMS	Short message service
SOP	Standard operating procedure
SUSAR	Suspected unexpected serious adverse reaction
SWAT	Study within a trial

THR	Total Hip Replacement
TMG	Trial management group
UKCRC	UK Clinical Research Collaboration
WPAI	Work Productivity and Activity Impairment

1. Protocol synopsis

Primary aim	To determine the long-term effectiveness and cost-effectiveness of hip implant types for younger patients undergoing primary elective total hip replacement (THR) using an efficient randomised controlled trial (RCT) design.
Trial design	Multi-centre, three-group, superiority randomized controlled trial with patient-level randomization, internal pilot, embedded qualitative research, and economic analysis.
Setting	60-100 hospitals across the UK
Target population	Adults <70 years undergoing THR for osteoarthritis
Inclusion criteria	• Between 18 and 69 years of age • Undergoing primary elective THR due to osteoarthritis
Exclusion criteria	• Not willing to consent • Receiving primary THR for reasons other than osteoarthritis (e.g., rheumatoid arthritis, etc.) • Patients requiring custom-made implants • Non-elective patients • Patients who lack capacity • Patients paying privately for their surgery • Prisoner
Randomisation and blinding	Patients will be randomised to receive either a cemented, uncemented or hybrid hip implant, in a 1:1:1 ratio. The trial will not be blinded.
Interventions	Cemented (reference), uncemented and hybrid hip implants.
Primary outcome	Revision at 10 years after randomisation
Secondary outcomes	Cost-effectiveness, quality of life, function and resource use

Follow-up	Participants will be asked to complete follow up questionnaires at 6-months, 12-months post-randomisation, and yearly thereafter.
Number of patients	7,866 participants
Duration of study	48 months, including set-up and internal pilot; and a minimum 10-year follow up
Nested qualitative study	During the internal pilot, recruitment consultations for up to 50 patients will be audio-recorded. Telephone interviews will be conducted with 20 patient participants, and 25 staff involved in trial recruitment (clinicians and research nurses)

2. Plain English summary

Background

Over 100,000 hip replacements are performed each year in the UK. Around 90% of patients report good pain relief and mobility after surgery, and most implants last 25 years or more. Primary hip replacement involves replacing a damaged hip joint with an artificial implant that has two main parts. One part goes into the thigh bone and ends in a ball which fits into a socket or cup attached to the pelvis, making a ball-and-socket joint. Implants can be fixed to bone with cement (cemented), without cement (uncemented), or cemented in the thigh bone and uncemented in the pelvis (hybrid). Cost ranges from £500 for some cemented to £2,000 for some uncemented implants. When an implant fails, for example, due to loosening or wear, it has to be re-done (revision surgery). Revision is a major operation, typically costing the NHS over £10,000 and it doesn't give patients the same benefits as first time surgery.
Cemented hip implants are safe, inexpensive, have a long track-record, and offer the best value-for-money for men aged over 75 and women aged over 65 years. There is no high-quality evidence to suggest more expensive uncemented or hybrid implants are any better than cemented implants for younger patients. Yet three quarters of NHS patients aged under 70 years receive uncemented or hybrid implants.

Design and methods

This is a clinical trial in patients aged 69 or younger who are having a total hip replacement. The trial is trying to find out which type of hip implant is best for patients under 70. Patients who agree to take part will be randomly assigned to receive an uncemented, cemented, or hybrid implant. Patients will be asked to complete questionnaires before and after their surgery. The questionnaires will continue every year for at least 10 years. Study patients will also be asked for their permission to access their medical data from other patient databases to follow them up for 10 years. This information will help us to find out whether any of the three implant types (cemented, uncemented or hybrid) leads to fewer revision surgeries for patients under 70. We will also find out whether there are any cost differences between the implant types. We will ask for more funding after the trial to follow-up patients beyond 10 years.

Patient and public involvement and engagement (PPIE)

Patient voices are central to our research. We have set up a PPIE group of patients with lived experience of hip replacement surgery before 70 years and have invited one of these patients to join our research team. We will meet regularly with patients in our groups and in the community to work on research design, management, and dissemination.

Dissemination

We will share our findings with patients, surgeons, and decision-makers to inform clinical practice, patient benefit, and commissioning of THR surgeries.

3. Background

3.1 Why is the research important?

Total hip replacement (THR) is one of the most clinically effective and cost-effective operations performed worldwide[1]. Three quarters of primary THRs last 15-20 years; 58% last up to 25 years[2]. There were more than 100,000 primary elective THRs performed in the UK in 2019[3, 4]. Half of these were performed in patients under 70 years, and 90% due to osteoarthritis.

THR is a major operation with a considerable recovery period. It takes, on average, ten weeks to return to work after THR,[1] and 6-12 months to experience the full benefits of the operation[5, 6]. Using the most clinically effective and cost-effective implant types for the increasing number of younger patients undergoing THR has the potential to impact on patients and their families, the NHS and society.

There are many implants for use in THR[7]. One key way in which these implants vary is in how they are fixed to the bone. Cemented implants have both the cup and the stem components fixed to the bone with cement. Uncemented implants rely on the bone bonding directly to the implant. Hybrid implants pair a cemented stem and uncemented cup.

The femoral stem has a metal or ceramic head which articulates with the liner of the cup which is normally made of ceramic or polyethylene. The different components of the implant and fixation compose the implant "construct", but we are referring to constructs as implants in this protocol for simplicity. Cemented metal-on-polyethylene THRs are the cheapest (£500-800) and have a long track record of use worldwide[8]. Newer materials and different fixation methods have been developed in an attempt to improve long-term patient outcomes[1], but at higher cost. An uncemented ceramic-on-ceramic implant costs around £2,000. Current NICE guidance (TA304) is based on revision rates of implants but does not advise how to choose between the different implant types available.

Implant failure often requires further surgery to replace the implant, causing pain, reduced function and reduced quality of life[9]. Marques and colleagues estimated that the NHS will spend more than £6 billion on primary THR surgeries in the next decade, including £1.2 billion on implants, and £900 million on revision surgery.

3.2 Rationale

Our NIHR-funded Hip Implant Prosthesis Study (HIPS) showed that cemented metal-on-polyethylene THRs are the most cost-effective option in men >75 and women >65 years[10]. For younger patients, the evidence is unclear; uncemented and hybrid implants are considerably more expensive, but randomised controlled trial (RCT) evidence for better

outcomes is lacking[11]. In the largest review of RCTs[11], we found no evidence that other implants had lower revision rates than cemented metal-on-polyethylene implants. More recent work shows that cemented implants perform better regardless of hospital or surgeon expertise[12].

HIPS results were widely disseminated in 2018-2019. They sparked an NIHR signal[13], and a BMJ editorial[14], highlighting the need for a rigorous RCT with long-term follow-up for younger patients. Other research [15, 16] also shows that uncemented implants are never the most cost-effective option. The National Joint Registry (NJR) reports year-on-year that revision rates for uncemented implants are not better than for other implants. This evidence, based on routinely collected data, is not reflected in clinical practice. Surgeons continue to use uncemented implants in 52% of the patients under 70 years, and 25% receive hybrid implants; these are more expensive and without evidence of additional benefit to cemented implants[10, 11, 17]. If surgeons switched to using more cemented implants, the NHS could save up to £30 million a year .

Current NICE guidelines advise using any implant with a 10-year revision rates (or projected rates) lower than 5% for primary THR. NICE were reluctant to change guidance after HIPS findings because evidence for the younger patients was not strong.

We invited surgeons from external hospitals to discuss our HIPS findings, how they were being received, and how to implement changes into practice. They pointed out some reasons for why change in practice may not happen:

- Some surgeons do not believe that uncemented implants would be worse for younger, healthier, more active patients; younger patients have higher levels of activity, and activity is not captured in registries; the observational evidence may not apply to “their” younger patients. Other countries, e.g., USA, Australia, Switzerland, use almost exclusively uncemented implants; there is no trial evidence showing which implant is best for younger patients in the long-term; clinical practice would only change on the basis of findings from a large clinical trial.
- Older patients are not expected to live as long after the operation, so surgeons are confident that any implant will outlast the remaining lifetime of the older patient[2]. There is more acceptance of the HIPS study results for the older patients, even though they agree these results may also be confounded by using registry data.
- Findings from further non-randomised studies that go against their usual practice are unlikely to drive substantial change. Surgeons would, however, incorporate findings from RCTs and cited examples of how previous RCTs had changed their practice, e.g. using more unicompartmental knee replacements following the TOPKAT trial[18], comparing them with total knee replacements.

- Surgeons with private practices mentioned how uncemented hip implants are perceived to be faster to perform, as they do not need to wait 20 minutes for cement to harden. If all surgeries run smoothly, they may fit one extra surgery in a theatre session, for additional financial benefit. There is no evidence on whether this time differential is real, or perceived, because uncemented implants are used on younger, healthier patients who may have had quicker surgeries anyway. This perceived "additional" time in theatre for cemented implants could indirectly make cemented implants more expensive. In a HIPS sensitivity analyses, we assumed that cemented surgeries took 45 minutes longer, and still cemented implants were the most cost-effective for all patients. In this Programme, we will be measuring theatre time for trial participants to settle this question with randomised evidence.

We have exhausted the methodological options for analysis of observational data to definitively answer the question of which implant type is best and most cost-effective for younger patients and have still not been able to adequately address selection bias with enough certainty to affect change in practice. This RCT is designed to influence national guidance for the patients who will, on average, live longest with the implants, minimising revisions, with potential savings for the NHS. Evidence from this RCT would allow patients and surgeons to make choices in true, shared decision-making, rather than differing to a surgeon's opinion or individual experience.

Other registry evidence shows that some hybrid implants have lower revision risks than some cemented implants for younger patients. However, all research based on registry data is affected by strong patient selection,[19, 20] which statistical methods cannot fully address. A definitive trial is needed to test the hypothesis (supported by some observational data) that uncemented or hybrid implants are superior to cemented ones in the long-term.

4. Aims and objectives

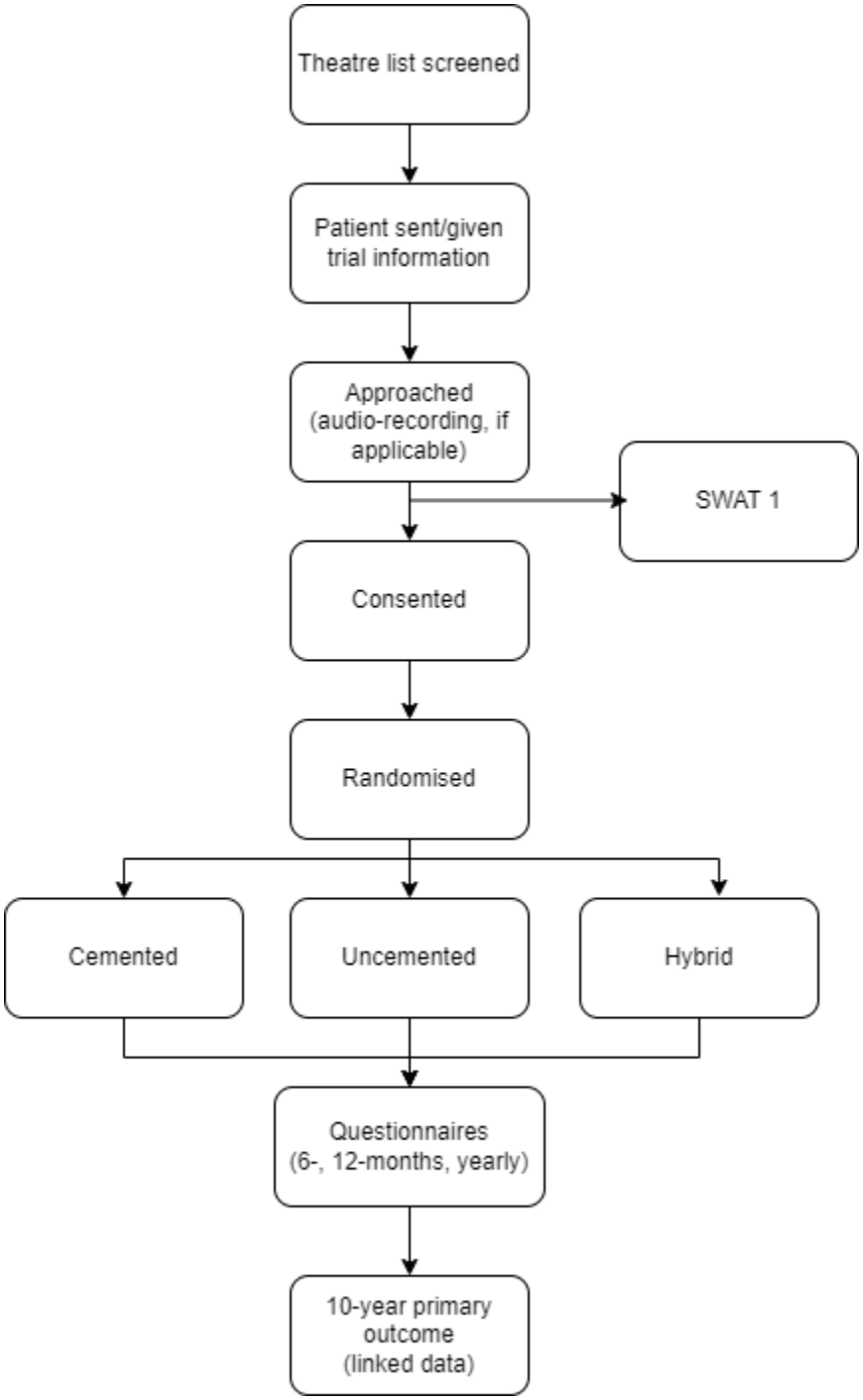
The HIPPY trial aims to determine the long-term effectiveness and cost-effectiveness of implant types for patients younger than 70 years undergoing primary elective THR. Specific objectives of the trial are:

A. To estimate the difference in the risk of revision 10 years after primary THR between uncemented and cemented, and hybrid and cemented implants.
B. To estimate the differences in secondary outcomes, including pain, function, health-related quality of life, and return-to-work up to 12 months after surgery between uncemented and cemented, and hybrid and cemented implants.
C. To estimate the cost-effectiveness of uncemented and hybrid implants compared with cemented implants.

5. Plan of investigation

5.1 Participant flow chart

Figure 1. Participant flow chart



5.2 Trial design and setting

The HIPPY trial is a multi-centre, three group, superiority randomised controlled trial (RCT) with patient-level randomisation, internal pilot, embedded qualitative research and health economic analysis. Patients undergoing THR will be randomised to receive either a cemented, uncemented or hybrid implant. The internal pilot will establish processes for, and test the feasibility of, recruitment.

The trial will be conducted at approximately 60-100 NHS hospitals, including independent sector centres treating NHS patients. All hospitals conducting elective primary THRs who have expressed an interest in taking part in the trial will be approached to take part, including sites with high ethnic diversity.

5.2.1 Key design features to minimise bias

Selection bias/allocation bias (systematic differences between baseline characteristics of the groups that are compared). This bias is ruled out by concealed randomisation (see Section 6.3), which will be performed as close to surgery as possible. The allocation will not be revealed until sufficient information to uniquely identify the participant and establish eligibility has been entered onto the trial database, and consent to be in the trial has been obtained.

Performance bias (systematic differences between groups in the care that is provided, or in exposure to factors other than the interventions of interest). This bias will be minimised by:

- Defining procedures for participant follow-up (see Section 6.5)
- Choice of primary outcome (revision surgery, see Section 5.5.1)
- Monitoring adherence to protocol (see section 9.2)

Detection bias (systematic differences between groups in how outcomes are determined). Patients will not be blinded to allocation as routine X-rays and other imaging may inform patients of which group they are in. The primary outcome is an objective measure (revision surgery) so should be unaffected by blinding. Some bias may be introduced in secondary outcomes, as many of these use patient reported questionnaire data..

Attrition bias (systematic differences between groups in withdrawals from a study).
This bias will be minimised by:

- Collecting primary outcome data from routinely collected data, the National Joint Registry. 96.2% of all primary and 92.5% of revision hip replacements performed in the UK were reported to the NJR as captured by the 2020/21 NJR data quality audit. The participant questionnaires also include questions about revision surgery to supplement where NJR data is not available.
- Implementing measures to promote trial acceptability ;

- Using established Bristol Trials Centre (BTC) methods to maximise the proportion of participants for whom all outcome data are available;
- Documenting non-adherence to random allocations;
- Using intention to treat (ITT) analysis and investigating sensitivity to attrition bias in statistical analysis (see Section 8);
- Implementing appropriate imputations for missing data, mostly relevant for costs and secondary outcomes (see Section 8).

Non-reporting bias (systematic differences between groups in non-capture of all revision surgeries)

- Sensitivity analysis around effect of non-reporting will be conducted
- Self-reporting of surgeries will be encouraged, especially if done privately or not at the location of the initial surgery (e.g. in another country)

Reporting bias will be minimised by having pre-specified outcomes (see Section 5.5) and pre-specified Statistical Analysis Plan (SAP) and Health Economics Analysis Plan (HEAP), which will be finalised before the database is locked (see Section 8).

5.3 Trial population

The trial population will be adults aged <70 years listed for elective primary THR due to osteoarthritis.

5.3.1 Inclusion criteria

Patients will be eligible for the trial if ALL of the following apply:

- Between 18 and 69 years of age (inclusive) at the time of screening
- Undergoing primary elective THR due to osteoarthritis (patients may also have other indications for THR in addition to osteoarthritis)

5.3.2 Exclusion criteria

Patients may not participate in the study if ANY of the following apply:

- Not willing to consent
- Receiving primary THR **exclusively** for reasons other than osteoarthritis (e.g., rheumatoid arthritis, etc.),
- Patients requiring custom-made implants
- Non-elective patients
- Patients who lack capacity
- Patients paying privately for their surgery (including patients using health insurance)
- Prisoner
- Patients who have previously been randomised to the HIPPY trial

Participants undergoing same day bilateral THR are eligible to take part in the trial. Only one hip will be randomised to the HIPPY trial. The surgeon or local research team will need to indicate which hip (left/right) will be randomised before randomisation can take place (see section 6.3).

5.4 Trial interventions

Participants will be randomised to one of the three following groups:

- Cemented implants
- Uncemented implants
- Hybrid implants

Surgeons will have discretion about combinations of bearing surface material and femoral head size. Choice of implant will not affect any aspect of care (e.g., rehabilitation).

5.4.1 Pre-requisites for clinicians and sites participating in HIPPY

Sites must stock at least two of the three implants to be able to take part in HIPPY.
Surgeons must be willing to randomise to at least two of the three implants to be able to take part in the trial. Surgeons will not be able to change the groups they randomise to throughout the course of the trial.

5.4.2 Cemented implants (control group)

Both the femoral and acetabular components are attached to the bone with cement. Polymethylmethacrylate or bone cement is used to fix the stem and cup in position. Surgeons can use any brand and type of cement.

5.4.3 Uncemented implants

The femoral and acetabular components attach to the bone by osseo-integration (bonding at a molecular level directly between bone and implant). They are usually press-fit and rely initially on a tight fit of the implants within the bone. Most uncemented implants are coated with substances such as hydroxyapatite which encourage growth of the patient's bone onto the implant.

5.4.4 Hybrid implants

The femoral component is cemented, and the acetabular component is uncemented. It allows for a variety of uncemented acetabular bearing surfaces including ceramics but paired with a cemented stem.

5.4.5 Interventions available as part of the usual care pathway

All three types of implants are available as standard of care within the NHS. However, some surgeons or sites may not use all three implants routinely and may only randomise patients between two groups. We will work with sites to obtain agreements to procure additional implants to their usual stock to be able to take part in this trial if required.

5.5 Primary and secondary outcomes

Primary and secondary outcomes are based on the core outcome set for trials in the field of joint replacement. A schedule of data collection is provided in Section 6.6.

5.5.1 Primary outcome

The primary outcome will be revision or not (including death without revision) at 10-years post-randomisation, defined by linkage with the NJR and/or Outcome Registries Platform (ORP) and triangulating with Hospital Episode Statistics (HES) revision OPCS4 codes and ONS records (or other region specific equivalents) for death. Where NJR, ORP or HES data are not available, participating sites may be contacted to enter these data manually on the trial database.

5.5.2 Secondary outcomes

Key secondary outcomes:
Cost-effectiveness of the three implant types at 10 years and for the remainder of the patients' lives. In secondary analyses cost-effectiveness will also be estimated for implants characterized by fixation and bearing surface.

Other secondary outcomes will include:

A) Yearly revision rates (descriptive) until last follow-up of the trial. These data will also be collected directly from patients on annual questionnaires to triangulate with or supplement our primary outcome data collection methods. After primary outcome at 10-years, further funding will be sought to collect revision rates using linkage to routine data at 5 years intervals from then onwards.
B) QALYs (Quality-adjusted life year): patient-completed EQ-5D-5L (baseline, 6-months, 12-months post-randomisation and annually thereafter). The trial questionnaires will be complemented by linkage with the national PROMS database for EQ-5D-3L at baseline and 6-months after primary and revision surgeries for trial patients
C) Pain: Hip disability and osteoarthritis outcome score (HOOS-12) pain scale (baseline, 6- and 12-months post-randomisation)
D) Activity: HOOS-12 activity limitations daily living score (baseline, 6- and 12-months post-randomisation)
E) Function: Oxford hip score (OHS) collected from linkage with national PROMS database at baseline and 6 months after primary and revision surgeries for trial patients.

F) Capability measure: ICECAP-A (baseline, 6- and 12-months post-randomisation)
G) Return-to-work and usual activities: bespoke questionnaire about absenteeism and presenteeism at 6-months post-randomisation, and the WPAI questionnaire at 12-months post-randomisation
H) Resource use (initial patient stay, 6- and 12-months post-randomisation)
   - o Operation details and implant type (e.g., theatre and recovery time)
   - o Date of admission and discharge for the initial operation and readmissions
   - ○ Procedure codes, health care resource use codes, and any other details of treatments and tests received when admitted.
   - o Additional health and social care resource use, including community-based health and social care resources, productivity losses and carer burden, will be collected in trial questionnaires at 6- and 12- months.

5.6 Sample size calculation

The trial will be powered to detect a 2 percent points difference (3% vs 5%) in the 10-year revision risk between the cemented arm and the uncemented arm and between the cemented arm and the hybrid arm.

A sample size of 7,866 participants (2,622 participants/group) is required to detect a target difference of at least 2% (3% vs 5%) in the 10-year revision risk with 90% power and 2.5% 2-tailed significance to account for two hypothesis tests, and assuming 10% linkage failure at 10 years (I.e. failure to link participant ID with NHS Digital or ONS register).

6. Trial Methods

6.1 Participant screening and recruitment

6.1.1 Initial identification and screening

Clinical lists/diaries will be screened by a member/s of the direct care team to identify potentially eligible patients who are scheduled for elective THR surgery. Before approach, the patient should be reviewed and assessed against the trial inclusion and exclusion criteria.

A member of the direct care team will make initial contact with patients regarding participation. Where site research teams are not considered part of the direct care team, the trial can be introduced to patients by their clinician who will ask the patient whether they give verbal consent for a member of the research team to contact them about the HIPPY trial. This should be clearly documented by the direct care team in the patient's medical records.

Potentially eligible patients will be provided with a study information pack, comprising an invitation letter/text and a patient information leaflet (PIL). The invitation letter/text and PIL can be provided to patients on paper or electronically, via text or email. The PIL will contain a link and QR code to the trial website where patients can access a short video to supplement the information they have received in the PIL, and additional written information (Supplementary Participant Information). The Supplementary Participant Information will also be available on paper for those who request it.

A member of the research/ clinical team, trained in the trial protocol, will then follow-up with a conversation/phone call/video call to discuss the study further and answer any questions they may have.

Patients who are contacted and do not want to find out more about the study will be asked if they would be willing to briefly give their reasons. Some sociodemographic data (age, sex, ethnicity and postcode for deprivation index) on non-participants will be collected to monitor inclusivity. The postcode will be entered onto the trial database to identify the deprivation index and then will be removed from view for the research teams (it will be available only in the database audit logs).

Patients who decline taking part in the trial will be invited to provide consent for their routine data to be collected from linked HES/PEDW/NJR/ORP/PROMS/ONS (or equivalent regional) databases as part of a study within a trial (see section 6.10)

6.1.2 Recruitment consultation

If a patient appears to meet the eligibility criteria and is interested in taking part in the study, the local care team will complete a recruitment consultation (this may involve arranging a different time / place that is more convenient for the patient). The recruitment consultation may take place in person (e.g. at the hospital), or it may be via an online video call or telephone call. This recruitment consultation may be audio-recorded (see section 6.2.1).

6.1.3 Consent

Patients who are willing to participate will be asked to provide informed, written consent, either electronically (eConsent) or on paper. Where an eConsent form is used, participants will not be asked to initial against each statement; instead, yes/no radio buttons will be used to indicate that they have read and agree to each statement. Where the patient has capacity but is unable to indicate their consent by marking a document, their consent may be given orally in the presence of at least one independent witness (i.e. someone not related to the trial) and recorded in writing (as eConsent or on paper). Where possible, reasons for declining participation will be recorded on the patient electronic case report form (eCRF) and will inform any changes to recruitment procedures if needed.

Patients can provide written informed consent face-to-face or remotely. If providing consent remotely, patients will be asked to complete an eConsent form. If patients are unable to complete a consent form electronically, patients can be provided with a paper consent form by post. The completed paper consent form will be returned to the local site team, and a member of the local site team will countersign the form. In these instances, the date the participant signed the form and the date the form was countersigned may differ.

Where an eConsent form is used, the original consent form will be stored on the trial database and two copies of the consent form will be required: (1) to be provided to the participant; (2) to be filed with a copy of the PIL in the participant's medical records. If the consent form is not completed electronically, as well as the two copies above, a copy of the paper form should also be scanned and uploaded to the trial database and the original paper copy stored in the Investigator Site File.

Site staff should also document key details of the informed consent process in the participant's medical notes.

6.1.4 Questionnaire

Participants will be asked to complete a baseline questionnaire before their surgery (as close to randomisation as possible). Baseline questionnaires will include the EQ-5D-5L, ICECAP-A, HOOS-12 and working status questionnaires. Baseline questionnaires can be completed online or over the phone with a member of the research team.

6.1.5 Inclusivity

A key ambition of HIPPY is to make participation as inclusive as possible, in particular including patients from under-served groups, those that are underrepresented in medical research (e.g. patients with autism and learning disabilities), those whose first language is not English and those from lower socioeconomic groups. Strategies to achieve this include provision of third party translation services for those unable to communicate in English language and offering key participant materials in a range of different languages. During the internal pilot, we will attempt to establish the need for translation of trial specific materials for use during the main phase of the trial. In this trial, being unable to speak or understand the English language is not an exclusion criterion.

The trial will also be recruiting from sites across the whole of the UK, including sites which may not have significant research infrastructure at present. Additional examples of inclusivity are outlined throughout this protocol (and/or other trial-related documents and delivery) and include consideration for key factors such as (but not limited to) social and economic factors.

To monitor for equality, diversity and inclusivity of the HIPPY recruitment process, age, sex, ethnicity and postcode (for deprivation index) will be collected on all participants screened,

identified as eligible, approached and recruited, including potential participants excluded at each stage with reasons why.

6.2 Qualitative research

Qualitative research will be conducted in the internal pilot to evaluate trial acceptability and equipoise and facilitate improvements in communication about the trial to optimise recruitment.

6.2.1 Audio-recording of recruitment consultations

During the pilot phase, patients and staff from selected sites will be approached for written consent to audio-recording of their recruitment consultation(s), but if a patient declines to be audio-recorded the recruitment consultation for the main trial will still take place. With patient consent, we expect up to 50 recruitment consultations will be audio-recorded across approximately 20 sites, chosen to reflect diversity in the population they serve.

6.2.2 Patient interviews

Audio-recorded telephone interviews, with an experienced qualitative researcher from the University of Bristol, will be conducted with around 20 patient participants at selected sites in the pilot phase to elicit patient equipoise and understanding of trial procedures, acceptability of trial recruitment pathways, and the quality of patient information, including the risks and benefits of participating in the trial. As part of the approach for consent to the main trial during the pilot phase, patients at sites taking part in the embedded qualitative study will be asked to indicate whether they are willing to take part in an audio-recorded telephone interview of up to 30 minutes. If they agree, then approximately 4 weeks after they consent to be part of the trial, a qualitative researcher will contact them and arrange to speak at a time and date convenient to them. In addition to providing written consent on the main trial consent form, the researcher will reiterate the study information and ask participants to re-affirm their consent verbally prior to commencing the interview. The interview topic guides have been developed in collaboration with PPIE group members and will focus on broad areas including the patient experience of recruitment, their understanding of the trial processes, influences on their decision to participate, perception of risks and benefits of participation, and any shift in equipoise. The topic guides will be flexible and iterative to ensure that any relevant issues raised by participants can be discussed and reflected on with other participants.

6.2.3 Clinician interviews

Audio-recorded telephone interviews will also be conducted with up to 25 surgeons and/or recruiting staff (including PIs at the sites) across selected trial sites. This will allow understanding of the surgeon's/recruiter's experience of participating in the trial, acceptability of trial processes, any challenges to recruiting patients, and any shift in equipoise. Surgeons/recruiters will be given/sent a participant information leaflet and consent form when

they first become involved in the trial to grant permission to audio-record their recruitment consultations and consent to an interview. The participant information leaflet will include contact details of the researcher should the participant wish to discuss any aspect of the study before deciding whether or not to participate. If they consent to take part in an interview (not consenting to interview will not preclude them from participating in the trial) the qualitative researcher will contact them to arrange a mutually convenient time for this to take place. At the beginning of the interview, participants will be asked if they have any questions before verbally reaffirming their consent.

6.2.4 Analysis and reporting of qualitative research

All audio-recordings of recruitment consultations (including both those who agreed or declined to take part in the trial) will be transcribed by a University approved transcription company, then anonymised by the research team, and subjected to rapid descriptive analysis by an experienced qualitative researcher. Analysis will focus on identifying interactions related to issues such as trial interventions, randomisation processes, how information about the trial is conveyed, patients' questions, requests for extra information/clarification and any misconceptions or notable comments. Audio-recordings of patient and surgeon / recruiter interviews will be transcribed and anonymised in the same way, and then subjected to thematic analysis [21] by a qualitative researcher. A sample of transcripts will be double-coded by another member of the research team. Findings from the rapid analysis of the qualitative work will be regularly reported to and discussed by the Trial Management Group (TMG), Programme Steering Committee (PSC) and PPIE group. This will ensure that any issues relating to participant equipoise, trial information, or the acceptability of recruitment and randomisation are reviewed in a timely fashion to ensure smooth implementation of any necessary improvements in trial processes. Reports will also be used to inform and update training sessions for recruiters.

6.3 Randomisation

Participants will be randomised as close to their surgery as possible. Randomisation will be performed by an authorised research team member using a third-party secure internet-based randomisation system (Sealed Envelope Ltd). The randomisation system will require key information to identify the participant to be entered before disclosing the allocation, ensuring allocation concealment. Participants will be randomised to receive a cemented, uncemented or hybrid implant. Participants may be randomised between either two or three implant types, depending on the site/ surgeon performing the surgery (see section 5.4). Patients will be randomised using permuted block randomisation stratified by site and surgeon using a 1:1:1 ratio for patients eligible to be randomised to 3 arms or 1:1 for those eligible to be randomised to any combination of 2 arms.

Participants undergoing same day bilateral THR are eligible to take part in the trial. Only one hip will be randomised to the HIPPY trial. The surgeon or local research team will need to indicate which hip (left/right) will be randomised before randomisation can take place.

The planned surgery date will be captured on REDCap. If a participant is randomised, and their surgery is postponed, the participant will retain their original allocation.

The number of patients allocated to each arm will be monitored throughout the trial by the TMG, PSC and Data Monitoring Committee (DMC). If there is an imbalance between groups, the allocation ratios may be amended to balance numbers of patients equally allocated to all three interventions. Any changes to the allocation ratio in response to recruitment patterns will be made in agreement with the PSC and DMC; up to three adjustments will be considered. Balance in the clinical and demographic characteristics of patients allocated to each arm will be monitored by the DMC.

6.4 Blinding

Participants, clinicians and the central research team will not be blinded to the allocation.

6.5 Timing and frequency of follow-up

Participants will be followed-up for at least 10 years after randomisation. Participants will be asked to complete outcomes assessments at 6-months and 12-months post-randomisation, and yearly thereafter for up to 10 years. Follow up will include the following questionnaires:

- EQ-5D-5L questionnaire at 6-months and 12-months, and yearly thereafter
- Hip disability and Osteoarthritis Outcome Score (HOOS-12) pain scale at 6- and 12-months
- HOOS-12 activity limitations daily living score at 6- and 12-months.
- ICECAP-A at 6- and 12-months
- Bespoke questionnaire about absenteeism and presenteeism at 6-months
- WPAI questionnaire at 12-months
- Resource use questionnaire at 6- and 12- months.

Participants will also be asked about whether have had any further hip surgery. If participants report further hip surgery on their questionnaire, and the central team is not able to link to data from routine patient databases, the central trial team may contact the participant to collect further information.

The trial aims to be as paper light as possible. Questionnaires will be completed preferably online, or over the phone with a member of the research team. Completion rates for

questionnaires will be monitored and in the event of low return rates or technical difficulties, questionnaires may be completed on paper. Email/text reminders will be sent approximately 2 weeks after the relevant timepoint if no reply has been received. Telephone data collection may be carried out for non-responders. We will aim to complete follow up within one month of the relevant time point where possible but will not exclude data collected after this point. Telephone follow-up will be carried out by the central trial team.

As well as sending reminders, participant newsletters and linked data will be used as strategies to maximise the proportion of participants for whom all outcome data are available.

6.5.1 Loss of capacity

Patients who lack capacity will not be eligible to join the trial. However, some participants may temporarily or permanently lose capacity during the follow up period. Participants will be assumed to have capacity unless advised otherwise.

If the trial team become aware that a participant has lost capacity during the follow period, the team will try to identify a suitable 'consultee' to provide advice on whether the participant would have wanted to continue participation. The consultee may be a Personal Consultee (e.g. friend or relative) or a Nominated Consultee (e.g. unpaid carer, an attorney acting under a lasting power of attorney, or a court-appointed deputy who has a relationship or personal knowledge of the person who lacks capacity). Where possible, a Personal Consultee will be identified. Where this isn't possible, the advice of a Nominated Consultee will be sought. The consultee must not be a member of staff working on the HIPPY trial and must be independent of the trial. The consultee will be provided with information about the trial and asked to complete a Consultee Declaration Form. Questionnaires will no longer be sent to the participant in the event of loss of capacity.

If someone declines the invitation to be a consultee, or advises against continuing participation, they will not be asked to sign anything. However, the research team will record, in the relevant study documentation and patient's medical records, that the person was asked and said no. This is so that they are not asked again about this role in the future.

The consultees advice will be followed accordingly. If they advise the research team that the participant should stop taking part in the trial, the research team must stop their participation in the trial, but any data collected up to that point will be retained.

Patients who regain capacity

If the trial team are advised that a participant has regained capacity during the follow up period, the participant will be provided information about the trial again. The participant will be invited to provide their ongoing consent when and if they are able. If the participant decides that they no longer want to take part in the trial, their participation in the trial will be stopped, but any data collected up to that point will be retained. Consultees will be informed of this

consent process following regained capacity as part of the Consultee Information Pack. Participants regaining capacity will not receive any further questionnaires, though with their ongoing consent, their data will be collected from patient databases / records.

6.6 Data collection

Data collection will include the following elements:

a.) A log of patients listed for THR and those who are sent/given a study information pack. Reasons for ineligibility and declining participation (when provided) will be recorded. Age, sex, ethnicity and postcode (for deprivation index) will be collected, where possible, from non-participants to characterise the population and monitor inclusivity.
b.) Consent to participate in the trial. Patients who can consent using electronic consent methods will be asked to provide their email address to the local care team to receive a link to the electronic consent form.
c.) Baseline characteristics, including sociodemographic data, co-morbidities, and previous hip surgery.
d.) Further baseline data collected via participant questionnaire completed prior to THR, including EQ-5D-5L, HOOS-12 and working status
e.) Allocation and operation details
f.) In hospital stay data
g.) Post-operative complications
h.) Follow up data collected via participant questionnaires (including EQ-5D-5L, HOOS-12, ICECAP-A, WPAI[22]and/or ModRUM), at 6- and 12-months, and [23]Patient satisfaction with treatment outcome (Likert scale) at 12-months
i.) Resource and health service use from randomisation to 1 year post randomisation using a bespoke version of the ModRUM questionnaire[24]
j.) Health care resource group (HRG) codes available from hospital finance or coding departments for patients in the trial from date of admission to 12 months follow-up, for all care provided by the centre, including initial hospital stay, readmissions, outpatient appointments, diagnostic tests and procedures.
k.) Linked NJR, national PROMS database, ORP and HES/PEDW (e.g. for outpatient, inpatient and emergency department (ED) care) and ONS mortality data during follow-up .

A schedule of data collection is provided in Table 1

Table 1. Data collection

	Screening & recruitment		Randomisation & intervention					
	Initial screening & consent	Post consent	0	Before discharge	6 months	12 months	Yearly	10 years
Initial screening data	X							
Consent	X							
Baseline data e.g. demography, medical history		X						
Allocation & operation details			X					
In-hospital data				X				
ED-5D-5L		X			X	X	X	X
HOOS		X			X	X		
ICECAP		X			X	X		
WPAI		X				X		
Resource and health service use				X	X	X		
Patient satisfaction						X		
Revision (primary outcome)							X	X
Adverse events				X	X	X		
HRG codes						X		

6.7 Source data

Source data will be the patient's medical records, the hospital's finance department codes for patients in the trial (HRG finance codes), where available; the patient's data routinely collected from national databases and registries (HES, PEDW, PROMS, NJR, ONS, ORP or other regional equivalents) and patient-reported questionnaires. Where information is not recorded anywhere else, the eCRFs will be the source data.

6.8 Planned recruitment rate

We plan to recruit patients from approximately 60-100 sites, with an estimated recruitment rate of five patients/site/month. We estimate that 90% of patients listed for THR under the age of 70 years will meet our eligibility criteria (OA as one indication for surgery) and 70% of those will be operated on by a surgeon willing to randomise to at least two of the implants in the trial. Of these, 60% of patients will agree to participate. Therefore, we anticipate approaching 8,957 patients per year to recruit and randomise 7,866 patients over 3 years.

6.9 Internal pilot

An 18-month internal pilot with embedded qualitative research will be conducted. All participants in the internal pilot will continue with follow-up and be retained in the full analysis. The relevant progress report to the funder (NIHR) will report on the progression criteria based on data up to month 18 of recruitment.

6.9.1 Progression criteria

A slower pace of recruitment is anticipated during the pilot phase due to a phased start across all sites during set up. Progression from the pilot phase to the main trial will depend on satisfying the following criteria by the end of the pilot recruitment phase:

Table 2. Internal pilot progression criteria

	Red	Amber	Green
Recruitment rate/site/month	≤3.2	>3.2 and <4.6	4.6
Number of sites opened	≤35	36 to 50	51
Total number of participants recruited	≤ 1509	1510 to 2156	2157
Percentage of randomised patients receiving allocated treatment	≤ 80%	>80% to <100%	100%

If all green criteria are met, the trial will proceed to the main trial with the same protocol. If ≥ 1 criteria are amber, adaptations to the protocol may be proposed. If ≥1 criteria are red, a discussion about whether the full trial is feasible will take place with the PSC and NIHR. If the progression criteria are satisfied, the remaining sites will be opened.

6.10 Study within a trial (SWAT)

6.10.1 SWAT 1: outcomes for non-participants

It is important to understand whether patients who consent to take part in research are different from those who do not consent. Patients who do not want to take part in the main trial will be asked for consent for their routine data, including NHS number and socio-demographic data, to be collected and analysed. For patients who consent to the SWAT, routine data, including their date of surgery, implant details, and revision surgeries and comorbidities, will be collected to monitor whether their outcome data differ from the patients in the main trial.

Our findings will not be powered to detect any difference in revision risks between patients who consent to the main trial and those who don't. The aim of this SWAT is to report any differences in outcomes between both groups to inform any health inequity concerns that may arise when designing our implementation strategy (i.e. methods or strategies to implement our trial results in real-world clinical practice).

SWAT 2: impact on caregivers

It is also important to understand the impact of primary THR on carers' health, wellbeing and productivity losses.

The follow up questionnaires will include questions to patients on whether they receive help or care from a relative, a friend, or support network. If so, patients would be asked whether they would be happy for us to send them a questionnaire for their helper/carer to complete.

For people who are helping or caring for trial patients, we will collect information on their own health care needs, and their forgone activities to support the THR patients, including time off work and leisure activities, and personal expenses using questionnaires, including the ModRUM Informal Care, EQ-5D-5L, Carer QoL, ModRUM Core Module. Costs, QALYs and productivity losses will be analysed using the same methodological framework as described in the economic evaluation methods for the trial patients' data in the main trial.

6.11 Discontinuation/withdrawal of participants

Participants are free to stop participating in any aspect of the trial at any time. All changes in participation, including reasons (where given), will be recorded. If a participant wishes to stop participating, data collected up until that point will be included in the analyses. Passive data collection (i.e., from medical records and national databases) will also continue, unless the participant expresses a wish for this to stop. This is explained in the PIL.

6.12 Site Communication

Investigator meetings will be held on a regular basis, with frequency to be decided by the site investigators and the TMG.

Trial newsletters will be distributed regularly to members of the research team and staff at participating sites to provide an update on trial progress and news. Where appropriate, participant newsletters may also be developed to encourage participant retention. These will be co-developed by the HIPPY PPIE group.

6.13 End of trial

The trial is part of a wider programme that is currently funded for 8 years, but the primary outcome is revision surgery at 10 years. The data analysis of the primary outcome will be performed at 10-years. Any additional reporting of outcome data will be provided only after agreement with the DMC, PSC, and the funder.
There is mounting evidence that hip implants perform well beyond the 10-year primary outcome date. We will continue to follow-up this patient cohort through linkage to their routine records (HES, PEDW, PROMS, NJR, ORP, ONS or equivalent regional registries) at further 5 year intervals (until death), subject to further funding being secured.

The trial may be terminated early on the instruction of the DMC or the results of another study supersede the necessity for completion of this study.

The end of the trial will be when all the data queries have been resolved, all linked data has been obtained and cleaned, the database is locked and the data set is ready for analysis

7. Safety reporting

Serious and other adverse events (AEs) will be recorded and reported in accordance with the Good Clinical Practice (GCP) guidelines and the Sponsor's Research Related Adverse Event Reporting SOP. Please see Table 3 for definitions.

Table 3. Safety definitions

Term	Definition
Adverse Event (AE)	An AE can be any unfavourable or unintended sign (including an abnormal laboratory finding), symptom or disease temporarily associated with the research procedure, whether or not considered related. AEs require continuous assessment.

Adverse Reaction (AR)	The distinguishing feature between an AR and AE is whether there is evidence to suggest there is a causal relationship between the event and the research procedure.
Serious Adverse Event (SAE)	Any untoward medical occurrence that: • results in death • is/was life-threatening • requires inpatient hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability/incapacity • consists of a congenital anomaly or birth defect Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant 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. NOTE: Hospital admissions are defined as overnight stays in hospital or day case admissions for surgery or care that requires use of a day case bed
Serious Adverse Reaction (SAR)	Any SAE that is classed in nature as serious and there is evidence to suggest there is a causal relationship between the event and the research procedure, but where that event is expected.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	Any SAE that is classed in nature as serious and there is evidence to suggest there is a causal relationship between the event and the research procedure, but where that event is unexpected.

The interventions in this study are three well-known and widely used types of implants. Many thousands of primary THR patients receive all the implants being compared in this trial per year. Adverse events (AE) are more likely to be related to the surgery (e.g. effects of anaesthesia) than the implant itself.

Details of all 'expected' AEs, including a description of the event and the date it started, will be recorded on the trial database, from the time of randomisation until discharge after surgery.

From the time of randomisation until 12 months post-randomisation, sites will be required to report all related fatal and 'unexpected' SAEs to the BTC within 24 hours of becoming aware of the event. The participant will be followed-up by the research team until the event resolves or until the end of the safety reporting period if the event is ongoing. The BTC will report all of

these SAEs to the trial Sponsor within 24 hours of becoming aware of the event. 'Expected' SAEs will not require expedited reporting to the Sponsor, unless they result in death and are deemed to be related to the intervention; they will be recorded on the database and reported periodically instead.

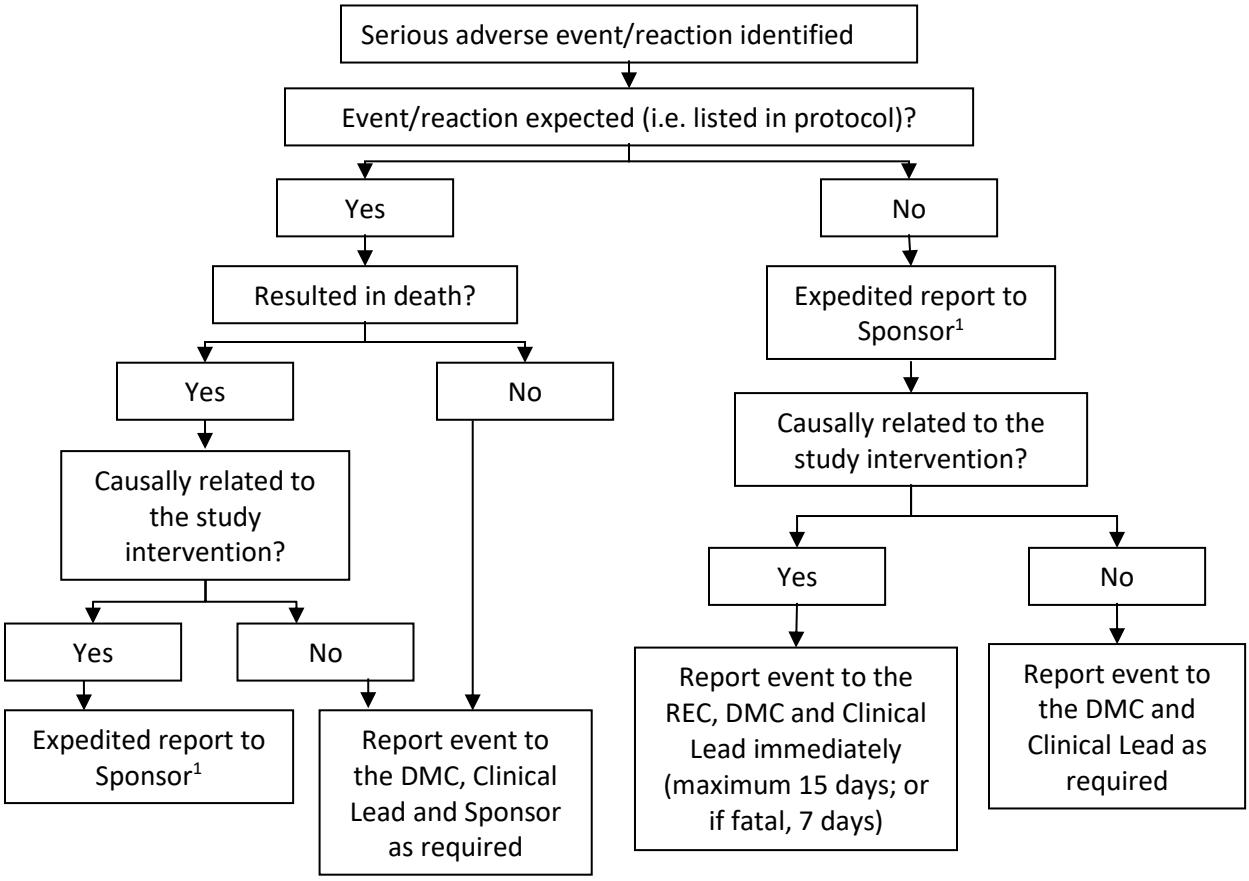
The "expected" events listed in Section 7.1 will likely require a hospital visit and/or admission and will be picked up from HRG finance codes at 12-months and at the end of the trial. Where HRG codes are not made available to the team, serious adverse events will be picked up from a review of patient's hospital medical notes at 12-months. SAEs may also be collected from patient questionnaires, and data linkage to NJR, ORP, ONS and HES/PEDW (or other regional equivalent) records.

Elective surgery during the follow-up period (e.g. elective primary joint replacement in other joints) that was planned prior to recruitment to the trial will not be reported as an unexpected SAE.

Further to this, BTC will report suspected unexpected serious adverse reactions (SUSARs) to the research ethics committee (REC), the DMC and the clinical lead, and copy all reports to the Sponsor, within 15 days (or 7 days, if fatal) of becoming aware of the event.
If the event is ongoing, there is no mandatory requirement regarding the frequency with which follow-up reports should be submitted. As a minimum, a follow-up report should be submitted when the event resolves/ends.

All SAEs will be reviewed by the Clinical Lead, DMC and Sponsor as required.

Figure 2. Serious adverse event reporting flow chart



[1]After 12 months post-randomisation these events do not need reporting to the Sponsor immediately but will be reported periodically, as required.

7.1 Safety reporting period

Data on expected adverse events will be collected from randomisation to hospital discharge.
All SAEs will be collected from randomisation to 12-months post-randomisation. All unexpected SAEs and related deaths from randomisation to 12-months post-randomisation will be subject to expedited reporting to the Sponsor.
Thereafter, all other SAEs will be reported to the Sponsor in periodic aggregated reports.

Expected adverse events

The following AEs occur frequently in patients undergoing hip surgery; they have been highlighted as adverse events following THR by expert healthcare professionals and will therefore be considered expected events. These only require expedited reporting to the Sponsor if they result in death and were related to the intervention:

- Bleeding
- Wound complication
- Thromboembolic disease
- Neural deficit
- Vascular injury
- Dislocation/instability
- Periprosthetic fracture
- Abductor muscle disruption
- Prosthetic joint infection
- Heterotopic ossification
- Bearing surface wear
- Osteolysis
- Implant loosening
- Cup-liner dissociation
- Implant fracture
- Reoperation
- Revision
- Readmission for hip-related conditions
- Death (within 90 days of THR)

Data on these adverse events collected during the trial will be reported regularly to the trial DMC and the Sponsor for review.

8. Statistics and data analysis

Statistical analysis

A detailed statistical analysis plan (SAP) will be written, including detail of all analyses that will be conducted following Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines.

Baseline characteristics of patients will be compared by reporting descriptive statistics; numeric variables will be summarised using means, medians, standard deviations and ranges as appropriate and categorical variables will be summarised using frequencies and proportions. These will be used to determine whether there are meaningful differences between the treatment groups at baseline and inform any subsequent sensitivity analyses adjusting for such imbalances.

The primary statistical analyses will be conducted on an intention-to-treat (ITT) principle, analysing patients in the groups to which they were randomised without imputing for missing

data. Revision risk will be analysed at 10 years follow-up (primary endpoint). Analyses will use mixed-effects logistic regression to estimate the effects of the interventions compared with reference implant (cemented) on revision risk, with centre and surgeons fitted as a random effect to take into account nesting of patients within these units. The results from this analysis will be presented as odds ratios and 97.5% confidence intervals (CIs). Risk difference and risk ratios will also be estimated using generalised linear regression and presented with 97.5% CIs. Patients who are eligible for only 2 arms of the study will be incorporated into the primary analyses using meta-analysis techniques. As well as formal comparisons between arms at 10 years follow-up, yearly revision risks will be described in each arm. The conventional threshold of 95% has been increased to 97.5% to account for the two treatment comparisons.

Sensitivity analyses will consider the impact of missing data and imbalances in clinical and demographic characteristics at baseline.

Subgroup analysis we will estimate revision risks by sex, age intervals (<60 and 60-69 years or at 5-year intervals if data allows) and bearing surface. These will be conducted by fitting interaction terms between age/sex and the allocation group and likelihood ratio tests will be performed to assess the strength of evidence against the null hypothesis of no effect modification.

Mixed-effects linear regression will be used to estimate the effects of the interventions compared with reference on scaled secondary outcomes (HOOS-12 and ICECAP-A) after transformation of the raw scores, if necessary, with centre/surgeon fitted as a random effect (as for the primary outcome). We expect some of these questionnaires to have ceiling effects (e.g., the HOOS-12), and in the presence of this we will consider alternative appropriate analyses including an analysis by whether patients have reached the best possible outcome or not or Tobit models.[25-29]
These will be pre-specified in the SAP prior to the end of follow-up.

Any further exploratory analyses will be prespecified in the SAP or HEAP.

8.1 Cost-effectiveness analyses

We will estimate the cost-effectiveness of the three trial implants in relation to QALYs for the remainder of the patients' lifetime. The economic evaluation will include an analysis of costs and outcomes over the 10-years of the trial and an economic decision model to extrapolate cost-effectiveness over the remaining lifetime of the patients. The primary analysis will take a health and social care payer perspective, with a societal perspective taken in secondary analyses.

We will draft a detailed health economic analysis plan (HEAP) and finalise it prior to primary outcome analysis. We will follow the most-up-to date NICE guidance to inform the analysis

methods in the HEAP. The reporting of the economic evaluation will follow guidelines at the time (currently the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) 2022)[30] guideline. The HEAP will be reviewed and will receive input from the PSC and DMC. Any changes or deviations from the original HEAP will be described and justified in the protocol, an updated HEAP, final report or publications as applicable, depending on the timing of the changes.

8.1.1 Trial-based cost-effectiveness analysis

The trial-based economic evaluation will estimate the costs, QALYs and cost-effectiveness for the first 10 years after THR. The primary analyses will be conducted on the intention-to-treat (ITT) population, as per statistical analyses of clinical outcomes.

During the first 12 months of the trial, we will use data collected from the trial records and patient questionnaires. Data capture systems will be designed to collect resources from medical records during the initial inpatient stay, and post discharge for a year at the treating hospital. Additional resource use on health and social care and productivity losses will be collected from the trial participants using online questionnaires completed at 6 and 12 months after randomisation. After 12-months, we will rely on linkage of trial patients to their records on HES/PEDW or other national equivalent routine data sources to collect resource use up to 10 years follow-up. Resources around the delivery of surgery will be micro-costed by linking with local hospital finance departments and sourcing national procurement implant prices available at the time of the analysis. All other resources will be macro-costed using national unit costs for health and social care and average weekly earnings available at the time.

QALYs will be valued from patients' responses to the EQ-5D-5L instrument using utility estimates for the UK population, using the most up-to-date guidance available at the time (currently[31]), and complemented by PROMS EQ-5D scores if trial data are missing but available on PROMS. QALYs will be derived using the area under the curve approach and adjusted for baseline utility and trial stratification variables, as per described in the HEAP.

We will also collect data from carers on their own quality of life, resource use, and time spent on informal care and on productivity losses due to providing informal care and analysed using the same methods as per trial patients data. Carers costs and QALYs will be included in the wider societal perspective for the economic evaluation.

Missing data will be imputing using multiple imputation methods, adjusting for socio-economic and baseline characteristics. Costs and QALYs will be discounted using NICE recommended discount rates (currently 3.5%) and estimated adjusting for stratification variables (e.g., bearing surface, trial stratification variables) and baseline utility for QALYs [32].

All relevant outcomes and costs (disaggregated by sector and perspective) will be reported in a cost-consequences table for a full, transparent, and wider view for decision-making. The cost-effectiveness parameter will be the incremental net monetary benefit statistics (INMB) using the NICE recommended thresholds (currently of £20,000 and £30,000 per QALY), and, if no arm is dominant, incremental cost-effectiveness ratios (ICERs), with appropriate consideration for uncertainty. We will perform a range of sensitivity analyses to the assumptions, methods, and model structure to explore the implications of uncertainty for decision-making.

In subgroup analyses we can further disaggregate implant types by bearing surface and patient group (under 60 years and 60-69 years of age). This analysis will aid in populating the economic model described below but has the limitation that bearing surface is not randomised, and therefore these analyses will provide estimates based on non-randomised data and not part of primary analyses.

8.1.2 Cost-effectiveness analysis beyond the trial

We will estimate lifetime cost-effectiveness using an economic decision model, by extrapolating revision risks, costs, and outcomes for the trial population beyond trial follow-up. The economic model will build on the previous economic model of the HIPS study [10] . In a primary analysis, the economic model will compare the three groups of cemented (reference implant), uncemented, and hybrid implants as per trial randomisation. Implants may be further characterised by fixation and bearing surface for more detailed cost-effectiveness comparison in secondary analyses. In subgroup analyses cost-effectiveness will be estimated by the population under 60 and 60-69 years of age.

The model parameters will be informed by revision rates, costs, and QALYs from the trial population complemented by analysis of NJR/PROMS/HES/PEDW/ORP or other national equivalent databases. Cost-effectiveness will be estimated using the mean incremental net monetary benefit (INMB) statistic for each implant compared to the reference implant, at the NICE-recommended willingness-to-pay threshold.[69] The implant with the highest INMB is the most cost-effective implant for each patient subgroup. In cost-effectiveness acceptability curves we will show how the probability of implants being most cost-effective varies as willingness-to-pay thresholds change.

9. Trial management

North Bristol NHS Trust will act as Sponsor. The trial will be managed by the Bristol Trials Centre (BTC). The BTC is a fully registered UK Clinical Research Collaboration (UKCRC) Unit. BTC will prepare all the trial documentation and data collection forms, specify the randomisation scheme, develop and maintain the study database, check data quality as the trial progresses, monitor recruitment and carry out trial analyses in collaboration with the investigators.

9.1 Day-to-day management

Appropriately qualified staff (by training) will be responsible for identifying potential trial participants, seeking informed participant consent, randomising participants, collecting trial data and ensuring the trial protocol is adhered to.

Day-to-day management of the trial will be overseen by the Chief Investigator (CI) and BTC staff. The Trial Management Group (TMG), consisting of the CI, Trial Manager and BTC staff, with other co-applicants and trial staff attending as needed, will meet approximately every 4-6 weeks (with smaller internal update meetings held on an ad hoc basis as needed). The TMG will monitor all aspects of the conduct and progress of the trial, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of the trial.

The TMG will meet with the Programme Group every 3-6 months, and more frequently if needed. All co-applicants will be invited to attend the Programme Group meetings. Meetings will be held with use of teleconference facilities to reduce environmental impact where appropriate.

9.2 Monitoring of sites

9.2.1 Site initiation

Before the trial commences, training sessions will be organised with sites by the BTC. These sessions will ensure that personnel involved in the trial fully understand the protocol, CRFs and the practical procedures for the trial.

9.2.2 Site monitoring

BTC will carry out central monitoring and audit of compliance of sites with the principles of GCP and data collection procedures. The trial database will have in-built validation and the TMG will review the completeness and consistency of the data throughout the trial. BTC will not check data entered onto the database against source data, unless there are good reasons to visit the site to complete a monitoring visit (e.g. the central monitoring highlights a problem or as requested by the sponsor).

9.3 Programme Steering Committee and Data Monitoring Committee

An independent Programme Steering Committee (PSC) and Data Monitoring Committee (DMC) will be established to oversee the conduct of the study. The membership will vary by committee but will include representation from surgeons, trialists, statisticians, health economists, qualitative researchers, and lay members. The CI, Trial Manager and other TMG

members as appropriate will attend PSC meetings, and a representative from the Sponsor (North Bristol NHS Trust) and NIHR will also be invited to attend. The PSC will meet regularly (frequency and format to be agreed by the PSC). The PSC will develop terms of reference outlining their responsibilities and operational details.

An independent DMC will be established to review safety data during the study and will advise on interim analyses. The DMC will agree a charter outlining their responsibilities and operational details. The DMC will meet (before or jointly with the PSC) before the trial begins and they will meet regularly thereafter (at intervals to be agreed with the Committee).

10. Patient and Public Involvement and Engagement

A PPIE group has already been established for the HIPPY Programme (which this RCT is part of), consisting of members with a range of socio-economic backgrounds and health status. The group have already contributed to the design of the study. Regular PPIE meetings will be held with the group for the HIPPY Programme. To facilitate the involvement of group members from across the country and those with mobility issues, the meetings will take place online. PPIE members will have an integral role in the trial development and oversight.

To complement the HIPPY PPIE meetings and to further promote diversity and inclusion, underserved groups will also be involved. As an example, the easy-read PIL will be co-produced with Brandon Trust to ensure documents are appropriate for patients with autism and learning disabilities. The trial team will also engage with people from other diverse communities/ community groups to understand cultural and other barriers to taking part in the trial, gain their views on the research and patient-facing materials.

The PPIE group and community group members will also be involved in the development of appropriate dissemination strategies and tools for diverse audiences.

Two patient representatives will join the PSC.

All patients and members of the public involved in research will be re-imbursed, following the NIHR payment guidance. The PPIE coordinator will be responsible for building and maintaining relationships with community group members, managing the PPIE group and provision of one-to-one support to patient representatives, as required.

11. Ethical considerations

11.1 NHS Research Ethics Committee and HRA approval

The research will be performed subject to a favourable opinion from an NHS REC and Health Research Authority (HRA), including any provisions of local site capacity and capability confirmation. Ethics review of the protocol for the trial and other trial related essential

documents (e.g. PIL and consent form) will be carried out by a UK NHS REC. Any subsequent amendments to these documents will be submitted to the REC and HRA for approval prior to implementation.

11.2 Risks and anticipated benefits

We do not anticipate any direct benefits to participants; however, the research will benefit future patients and the NHS by providing evidence on the effectiveness and cost-effectiveness of THR.

All the treatments in this trial are currently used in the NHS, therefore we do not anticipate any increased risk for trial participants compared with standard care.

11.3 Co-enrolment

Co-enrolment with another study will be considered by a member(s) of the HIPPY TMG on a case-by-case basis. Generally, co-enrolment will be allowed if the intervention is not expected to influence the primary outcome and it is not considered too burdensome for the patient.

12. Research governance

This study will be conducted in accordance with:

- GCP guidelines
- UK Policy Framework for Health and Social Care Research

12.1 Sponsor approval

Any amendments to the trial documents must be approved by the Sponsor prior to submission to the REC/HRA.

12.2 Confirmation of capacity and capability

Confirmation of capacity and capability from the local NHS Trust is required prior to the start of the study.

Any amendments to the study documents approved the REC and the HRA will be submitted to the study sites, as required by the HRA.

12.3 Investigators' responsibilities

Investigators will be required to ensure that local research approvals have been obtained and that any contractual agreements required have been signed off by all parties before recruiting

any participants. Investigators will be required to ensure compliance to the protocol and study processes and with completion of the CRFs. Investigators will be required to allow access to study documentation or source data on request for monitoring visits and audits performed by the Sponsor or BTC or any regulatory authorities.

Investigators will be required to read, acknowledge and inform their trial team of any amendments to the trial documents approved by the REC/HRA that they receive and ensure that the changes are complied with.

12.4 Monitoring

The study will be monitored and audited in accordance with the Sponsor's policy, which is consistent with the UK Policy Framework for Health and Social Care Research. All study related documents will be made available on request for monitoring and audit by the Sponsor (or BTC if they have been delegated to monitor), the relevant REC/HRA and for inspection by other licensing bodies.

12.5 Indemnity

This is an NHS-sponsored research study. For NHS sponsored research HSG(96)48 reference no. 2 refers. If there is negligent harm during the clinical trial when the NHS body owes a duty of care to the person harmed, NHS Indemnity covers NHS staff, medical academic staff with honorary contracts, and those conducting the trial. NHS Indemnity does not offer no-fault compensation and is unable to agree in advance to pay compensation for non-negligent harm.

University of Bristol hold insurance which covers harm caused by the conduct of staff & students. It also cover other agents of the University, if acting in accordance with University of Bristol instruction but not the negligence of 3rd party persons or organisations.

13. Data protection and participant confidentiality

13.1 Data protection

Data will be collected and retained in accordance with the UK Data Protection Act 2018.

13.2 Data handling, storage and sharing

13.2.1 Data handling

Full details will be provided in the data management plan, which will also define how personal identifiable and non-identifiable patient information is used in the study.

Data will be entered into a purpose-designed database hosted on the University of Bristol network. Database access will be password-controlled and restricted to HIPPY trial staff at the participating sites and the co-ordinating centre.

Some sociodemographic data (i.e. age, sex, ethnicity and postcode for deprivation index) will be collected for all screened patients for the purposes of inclusivity monitoring and identifiable information will be collected for all consenting participants.

Any information capable of identifying individuals will be held on a secure University of Bristol server. HIPPY trial staff at the coordinating centre will have access to this identifiable information. Within the main study database, participants will be identified using a unique study identifier. Other personal identifiers (name, address, postcode, contact number, NHS number) will also be held in order that study participants may be contacted during follow-up and provided with a summary of the results at the end of the trial, as well as for data linkage to routine patients databases (HES/PEDW/NJR/PROMS/ONS/ORP). Information capable of identifying participants will not be made available in any form to those outside the study, unless participants give permission (e.g. use of mobile phone numbers by a texting service). The database and randomisation system will be designed to protect participant information in line with data protection legislation. Trial staff will ensure that the participant's confidentiality is maintained through secure handling and storage of participant information at participating sites and in accordance with ethics approval.

Data will be entered promptly with data validation and cleaning to be carried out throughout the trial.

13.2.2 Data storage

All study documentation will be retained in a secure location during the conduct of the study and for five years after the end of the trial, when all patient identifiable paper records will be destroyed by confidential means. All audio-recording files will be retained in a secure location during the conduct of the study and for 12 months after the end of the trial, when these files will be deleted.

Archiving will be done as per BTC SOPs in agreement with the Sponsor. Sites will be expected to archive their own documents as per site agreements and BTC will archive the TMF and central coordinating centre documents for five years after the end of the trial.

13.2.3 Data sharing

Data will not be made available for sharing until after publication of the main results of the study. Thereafter, it is the authors' intention to share their underpinning research data in order to maximise reuse and evidence their findings. The data will be deposited at the University of Bristol Research Data Repository (data.bris.ac.uk/data) where once published, they will be assigned a doi: . A metadata record will be published openly by the repository and this record will clearly state how data can be accessed by bona fide researchers. Requests for access will be directed to the Research Data team at Bristol, who will assess the motives of potential data re-users before granting access to the data.

Where data has been obtained through data linkage with external registries, the relevant data sharing agreements will be observed (which may restrict some data sharing). A minimum requirement with respect to scientific quality will be a publicly available pre-specified protocol describing the purpose, methods and analysis of the secondary research, e.g. a protocol for a Cochrane systematic review. Anonymised recruitment consultation and interview transcripts may also be used to support teaching of qualitative research methods.

14. Dissemination of findings

The results will be disseminated through the usual academic channels (peer-reviewed journal publications and national / international conferences). We will target general medicine high-impact journals such as the BMJ and the Lancet for the trial findings. Where appropriate, we will liaise with press offices (e.g. the University of Bristol Press Office, North Bristol Trust Press Office, NJR, and NIHR ARC) to produce press releases for findings. We will share our findings with all the involved study centres, the NJR, and orthopaedic societies (e.g. British Orthopaedics Association, the British Hip Society, and the British Orthopaedic Clinical Directors Society, and the European Federation of National Associations of Orthopaedics and Traumatology).

We will work in partnership with patient groups (e.g. Centre for Public Engagement (CPE) and our HIPPY PPIE group) to identify appropriate dissemination tools and outlets, including videos, detailing our findings. Summaries of the results will also be disseminated to charities supporting patients with arthritis (e.g., Versus Arthritis, INVOLVE, websites of participating trust centres, and NJR Communication offices and the NJR website via the NJR PPI group.

Patients who state they would like to be updated on the results of the study will receive a summary of results at the end of the trial.

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16. Version History

Version	Date	Description of changes
1.0	21Mar24	Pre-approved version
2.0	20May24	First approved version
3.0	XXJul24	Addition of ORP database Clarification on how eConsent will be implemented and length of data storage. Clarification on how bilateral hip replacements will be recorded and managed. Addition of phone calls to participants to collect data on further hip surgery. Correction of typographical errors.