Feasibility study for a comparative trial of hybrid or cemented implants for total hip replacement.
Hip arthroplasty with Hybrid Or cemented implants: Patient reported outcomes

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Study Sponsor:

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Study Protocol Approval

I, the undersigned, hereby approve this clinical study protocol:

Authorised by Chief Investigator:

Signature: Please see email in lieu of wet ink signature **Date:** 30/04/2021

Professor Tim Board
Chief Investigator
Wrightington, Wigan and Leigh Teaching Hospitals
NHS Foundation Trust

I, the undersigned, hereby approve this clinical study protocol:

Authorised on behalf of Sponsor:

Signature: Please see email in lieu of wet ink signature **Date:** 05/05/2021

Professor Ian Trail
Clinical Director of Research
Sponsor Representative
Wrightington, Wigan and Leigh Teaching Hospitals
NHS Foundation Trust

I, the undersigned, hereby approve this clinical study protocol:

Authorised on behalf of University of Manchester:

Signature: Please see email in lieu of wet ink signature **Date:** 30/04/2021

Dr Martin Eden
Health Economist
University of Manchester

I, the undersigned, hereby approve this clinical study protocol:

Authorised on behalf of University of Manchester:

Signature: Please see email in lieu of wet ink signature **Date:** 30/04/2021

Dr Rachael Powell
Research Lead – Qualitative Study
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I, the undersigned, hereby approve this clinical study protocol:

Authorised on behalf of University of Liverpool:

Signature: Please see email in lieu of wet ink signature **Date:** 30/04/2021

Dr Richard Jackson
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I, the undersigned, hereby approve this clinical study protocol:

Authorised on behalf of University of Bristol:

Signature: Please see email in lieu of wet ink signature **Date:** 30/04/2021

Dr Vikki Wylde
Lead Investigator - PROMS
University of Bristol

General Information

For the purposes of clarity, use of the words 'Study' and 'Trial' are interchangeable and their usage will differ depending on the context in which they are used.

This document describes the HipHOP trial and provides information about procedures for entering patient, surgeon and other health professional participants into it. The protocol should not be used as an aide-memoir or guide for the treatment of other patients. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to the registered investigators in the trial.

This protocol defines the participant characteristics required for study entry and the schedule of treatment and follow-up. Participant recruitment will be undertaken in compliance with this document and applicable regulatory and governance requirements. Waivers to authorise non-compliance are not permitted.
Incidence of protocol non-compliance whether reported prospectively (e.g. where a treatment cannot be administered on a scheduled date as a result of public holidays) or retrospectively noted (e.g. as a result of central monitoring) are recorded as protocol deviations. These are monitored and reported to trial oversight committees

The trial is managed by the North West Surgical Trials Centre, which is embedded within the Liverpool Clinical Trials Centre (LCTC). Sites enrolling patients for the first time are advised to contact the LCTC to confirm they have the most up to date version. LCTC will refer clinical queries relating to this trial to the Chief Investigator or delegated other.

Statement of Compliance

This study is designed to comply with the principles of Good Clinical Practice (GCP) and will be conducted in compliance with the protocol, LCTC Standard Operating Procedures and the UK Policy Framework for Health and Social Care Research 2017 or the latest version of the relevant Research Governance Framework should it be revised and reissued.

UK Registration

This study will have Health Research Authority (HRA) and Research Ethics Service (RES) approval. All research sites will confirm capacity and capability to conduct the study and will complete an Organisation Information Document and a Research Site Agreement.

Contact Details: Institutions

Sponsor:	Trial Management and Monitoring:	Qualitative element: (Workstream 2)
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Contact Details: Individuals

Individual Authorised to Sign Protocol Amendments on behalf of the Sponsor:	**Chief Investigator (CI):**	**Qualitative Researcher:**
Clinical Director of Research Wrightington, Wigan and Leigh Teaching Hospitals NHS Foundation Trust Trust Headquarters Royal Albert Edward Infirmary Wigan Lane Wigan Lancashire WN1 2NN T: 01257 256 465 E: ResearchAdmin@wwl.nhs.uk	Professor Tim Board Consultant Orthopaedic Surgeon Wrightington Hospital Hall Lane Appley Bridge Wigan Lancashire WN6 9EP T: 01257 256 528 E: tim@timboard.co.uk	Dr Rachael Powell Division of Psychology and Mental Health School of Health Sciences University of Manchester Coupland 1 Building Oxford Road Manchester M13 9PL T: 0161 275 2569 E: rachael.powell@manchester.ac.uk
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Medical Expert who will evaluate SAE Reports	**Alternative Medical Expert who will evaluate SAE Reports 'Clinical Coordinator'**	**Alternative Medical Expert who will evaluate SAE Reports 'Clinical Coordinator'**
Chief Investigator Details as above	Professor Sion Glyn-Jones Consultant Orthopaedic Surgeon Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences University of Oxford Botnar Research Centre Windmill Road Headington Oxford OX3 7LD T: 01865 223 421 E: sion.glyn-jones@ndorms.ox.ac.uk	Mr Hiren Divecha Consultant Orthopaedic Surgeon Wrightington Hospital Hall Lane Appley Bridge Wigan Lancashire WN6 9EP T: 01257 256 528 **E:** hiren.divecha@doctors.org.uk
Medical Expert who will Advise on all Protocol Related Clinical Queries:	**Alternative Medical Expert who will Advise on all Protocol Related Clinical Queries:**	**Alternative Medical Expert who will Advise on all Protocol Related Clinical Queries:**
Chief Investigator Details as above	Mr Sunil Panchani Consultant Orthopaedic Surgeon Wrightington Hospital Hall Lane Appley Bridge Wigan Lancashire WN6 9EP T: 01257 256 251 E: sunil.panchani@wwl.nhs.uk	Mr Hiren Divecha Consultant Orthopaedic Surgeon Wrightington Hospital Hall Lane Appley Bridge Wigan Lancashire WN6 9EP T: 01257 256 528 E: hiren.divecha@doctors.org.uk

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Glossary

AE	Adverse Event
SI	Adverse Event of Special Interest
CI	Chief Investigator
CRF	Case Report Form
EQ-5D-5L™	EuroQol 5 Dimension, 5 Level Quality of Life Questionnaire
FJS	Forgotten Joint Score
GP	General Practitioner
HE	Health Economy / Economist
HRA	Health Research Authority
ISDMC	Independent Safety and Data Monitoring Committee
IEC	Independent Ethical Committee
MREC	Main Research Ethics Committee
OHS	Oxford Hip Score
PI	Principal Investigator
PROMS	Patient Reported Outcome Measures
RCT	Randomised Controlled Trial
R&D	Research & Development
SAE	Serious Adverse Event
SADE	Serious Adverse Device Event
SAPS	Self-Administered Patient Satisfaction scale
THA	Total Hip Arthroplasty
TSC	Trial Steering Committee
USADE	Unanticipated Serious Adverse Device Effect
WPAI-SHP	Work Productivity and Activity Impairment–Specific Health Problem
WS1	Workstream 1, (i.e. the quantitative element of the study (RCT))
WS2	Workstream 2, (i.e. the qualitative element of the study (Interviews))

1 ROLES AND RESPONSIBILITIES

1.1 Sponsor

Wrightington, Wigan and Leigh Teaching Hospitals NHS Foundation Trust is the Sponsoring organisation and is legally responsible for the study. They will centrally manage the budget and allocate funding to collaborators, and formally delegate specific Sponsoring roles to the Chief Investigator and Liverpool Clinical Trials Centre.

1.2 Funder

This study is funded by the National Institute for Health Research (NIHR) via their Research for Patient Benefit (RfPB) funding stream to the research cost value of £272,285.00.

The NIHR ratifies the membership of Trial Steering Committee (TSC). The role of the TSC is to offer support and advice to the Trial Management Group on behalf of NIHR, however NIHR had no role in the design of this study and will not have any role during its execution, analyses, interpretation of the data, or decision to submit results.

1.3 Chief Investigator

Professor Tim Board is the Chief Investigator for the trial and is responsible for overall design and conduct of the trial in collaboration with other members of the Trial Management Group.

1.4 Principal Investigators

In each participating site a principal investigator will be identified to be responsible for identification, recruitment, data collection and completion of CRFs, along with follow up of study patients and adherence to study protocol at site. They will also be responsible for safety reporting and processing any applicable safety information.

1.5 University of Liverpool

Liverpool Clinical Trials Centre (LCTC), the University of Liverpool's (UoL) Clinical Trials Unit, in collaboration with the Chief Investigator, will have overall responsibility for the management of activities relating to quantitative elements of the study, including (but not limited to) study planning, Trial Master File Management, safety reporting, data management, randomisation, statistical analysis and coordination of participating sites. LCTC will manage the budget allocated to UoL.

1.6 University of Manchester

University of Manchester in collaboration with the Chief Investigator, will have overall responsibility for the management of activities relating to qualitative and Health Economics elements of the study, including (but not limited to) study planning, data management and data analysis. UoM will manage the budget allocated to them.

1.7 University of Bristol

University of Bristol (UoB) in collaboration with the Chief Investigator, will have overall responsibility for the selection and rationale for use of the Patient Reported Outcome Measures (PROMs) questionnaires.

1.8 University of Oxford

University of Oxford (UoO) employs the NIHR Senior Researcher who is the named mentor of the HipHOP Chief Investigator. UoO will manage the budget allocated to them.

1.9 Trial Management Group (TMG)

A Trial Management Group (TMG) will be formed comprising the Chief Investigator, other lead investigators (clinical and non-clinical), members of the LCTC and Sponsor. The TMG is responsible for monitoring all aspects of the progress and conduct of the trial and will be responsible for the day-to-day running and management of the trial. The TMG will meet at least monthly at setup stage and then reduce to quarterly throughout the year unless more frequent meetings are required. See section 18.1 for further information.

1.10 Trial Steering Committee (TSC)

Membership of the Trial Steering Committee (TSC) will comply with NIHR guidance regarding its composition. The role of the TSC is to provide overall supervision of the trial and provide advice through its independent Chairperson. The decision for the continuation of the trial lies with the TSC and as such they will meet throughout the duration of the trial. See section 18.2 for further information.

1.11 Protocol Contributors

Table A below lists those who substantively contributed to the design of the protocol.

Table A: Main authors of this protocol.

Name	**Contribution to protocol**
Professor Tim Board[1]	Inception of trial, lead on the writing of the clinical elements for Workstream 1 (i.e. Randomised Controlled Trial).
Tony Coffey[2]	Protocol development, governance arrangements and trial conduct.
Dr Martin Eden[3]	Design of health economics component
Helen Hickey[2]	Reviewer for LCTC during protocol development.
Dr Richard Jackson[2]	Statistical input and methods of analysis.
Dr Cheryl Jones[3]	Design of health economics component
Dr Rachael Powell[3]	Design of qualitative interview research methods and data analysis.
Eftychia-Eirini Psarelli[2]	Statistical input and methods of analysis.
Dr Vikki Wylde[4]	Patient Reported Outcome Measures selection and usage.

[1]Wrightington, Wigan and Leigh Teaching Hospitals NHS Foundation Trust
[2]LCTC, University of Liverpool
[3]University of Manchester
[4]University of Bristol

2 PROTOCOL OVERVIEW

Title:	Feasibility study for a comparative trial of hybrid or cemented implants for total hip replacement. Hip arthroplasty with Hybrid Or cemented implants: Patient reported outcomes
Phase:	II
Sample size:	All participants will be recruited from the UK Quantitative Workstream ("Workstream 1") • 40 patients Qualitative Workstream ("Workstream 2") • Up to 30 patients • 20-30 surgeons • Approximately 9 health professionals
Inclusion Criteria:	Workstream 1 1. Age 18 years and above 2. Undergoing a primary total hip arthroplasty with either a fully cemented or hybrid implant[1] 3. Able to give informed consent prior to randomisation 4. Able to communicate in both written and spoken English Workstream 2 Patient sample: 5. Have been approached to take part in WS1. Surgeon sample: 6. Consultant orthopaedic surgeon at a Workstream 1 site or a potential site for a future full trial. Healthcare professional sample: 7. Involved in recruiting to Workstream 1 and/or collecting patient self-reported data.

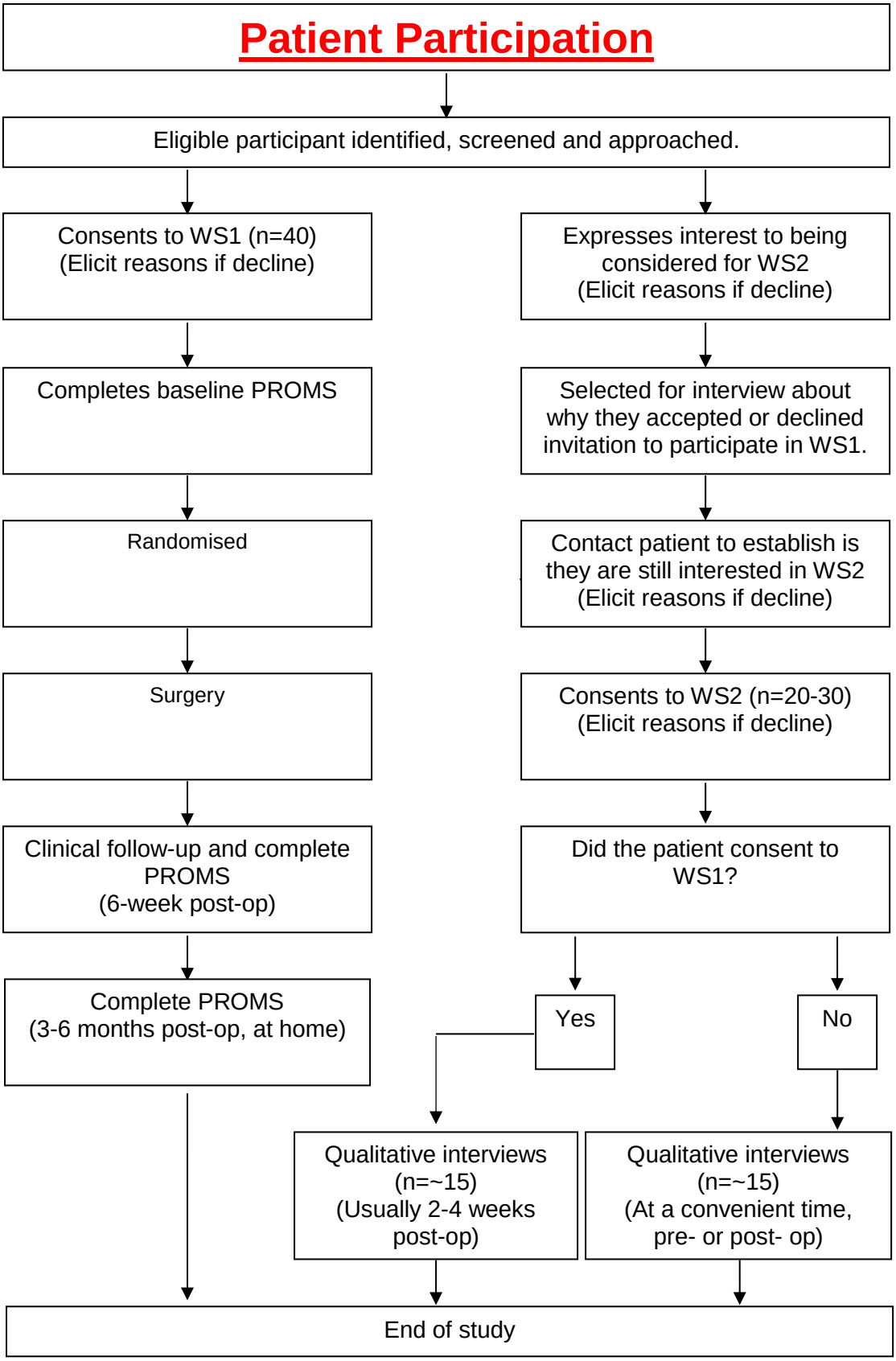
[1] All implants and bone cements that are used must be CE marked and used in accordance with their intended use. There is no limitation as to the manufacturer of prostheses used and surgeons will continue to use the implants that they are familiar with. Furthermore, surgeons will be free to use whichever head/socket material and diameter they feel appropriate. The surgical approach, anaesthetic type, rehabilitation after surgery and other concomitant factors will be as per the surgeons' normal care. These factors will be recorded.

Exclusion criteria:	Workstream 1 1. Previous surgery to the hip joint. 2. All procedures with an indication other than osteoarthritis 3. Patient requiring complex total hip arthroplasty surgery, specifically augmentation of the acetabulum (e.g. structural bone graft or metal augment) and/or shortening/de-rotational osteotomy of the femur at the time of surgery. 4. Patients requiring bilateral simultaneous total hip arthroplasty 5. Vision impairment that precludes the completion of PROMS questionnaires. Workstream 2 All participants: 6. Hearing impairment that precludes communication by standard telephone.
Number of sites:	Workstream 1: 3 sites Workstream 2: Between 3 and 6 sites
Study duration:	State duration per subject Workstream 1: • Patient will participate in the study for a maximum of 6 months post operation. Workstream 2: • All participants will participate in a single one-to-one interview, lasting approximately 30-60 minutes for patients and approximately 30 minutes for surgeons and other health professionals.
Objectives:	Workstream 1: Primary: To ascertain the feasibility of performing a comparative trial of hybrid or cemented implants for total hip replacement. Secondary: To Assess 1. Recruitment to a trial of this nature 2. Capture rate for postal/telephone follow-up 3. Rate of trial withdrawal 4. PROMS data statistics to determine the power required for the full study 5. Intra-operative and post-operative safety 6. To identify the incidence of treatment cross over during surgery

	7. To determine the feasibility of conducting a within-trial cost-utility analysis Workstream 2: 1. To understand patient experiences of the trial and their reasons for taking part or declining to participate 2. To understand surgeons' perceptions of the trial and equipoise, to establish factors underlying their willingness or unwillingness to participate in a trial, and to understand any barriers to implementation in practice of trial findings. 3. To understand health professionals experiences of recruiting participants to the trial and data collection, to learn about their thoughts regarding patient perceptions of the study, and to identify any changes that could enhance recruitment and running of the larger study.

Protocol Summary - continued

Schematic of Study Design for patient participants:



2.1 Introduction

Patient outcomes

Although THA offers generally good outcomes and is deemed a highly cost effective procedure[1], not all patients achieve their desired functional outcome[2]. Studies have shown that between 10-30% of patients may not improve following THA[2, 3]. Historical literature has focused on outcomes such as revision surgery and surgical complications and it is this that has driven implant evolution and patient selection. Whilst there is some evidence regarding the importance of physiological and psychosocial patient factors in determining patient-reported functional outcomes, there is very little evidence investigating the influence of implant type on functional outcome.

The James Lind Alliance has produced a list of the top 10 priorities for research in hip and knee replacement including the question "What (health service) pre-operative, intra-operative, and post-operative factors can be modified to influence outcome following hip and knee replacement?" Our study is aligned to this priority in that we are investigating the intraoperative factor of hip replacement type and its influence on outcome.

Current literature

The vast majority of orthopaedic studies are ranked level 3 or below on the level of evidence scale[4]. Literature searches have only identified a handful of randomized controlled trials (RCTs) comparing the outcomes of the different types of THA. A meta-analysis performed by Tsertsvadze et al, 2014, found there were only 4 RCTs looking at patient outcomes in terms of implant fixation[5-9]. Only one of these papers studied the functional outcome of UK patients. A consistent criticism of these RCTs is that they have inconsistent results, poor reporting and missing data thus reducing the power and validity of the conclusions that are presented. An extensive search of the NIHR portfolio and other trial registries (ClinicalTrials.gov, WHO International Clinical Trials Registry Platform, and the EU Clinical Trials Register) has been carried out and has not identified any studies similar to this proposal. There are a number of studies investigating aspects of individual manufacturer's implants or systems but these are very specific, non-pragmatic trials. There are studies investigating other aspects such as anaesthetic techniques and postoperative therapy.

A recent systematic review highlights this lack of published evidence concluding "This review highlights the need for new randomised controlled trials with rigorous reporting on core, adequately powered outcomes"[10]. The authors recommend that large and long-term pragmatic RCTs are needed before definitive conclusions are made regarding the effectiveness of the different types of implant and that authors specify the minimal clinically important differences and power calculations for their primary outcomes. It is noted that to improve the quality of reporting, authors are encouraged to conform to the recommendations outlined in the CONSORT (consolidated standards of reporting trials) statement[11] and its extension for RCTs evaluating non-pharmacologic interventions[12]. Adherence to the recent CONSORT extension on patient-reported outcomes measures (PROMs) would help to further improve the reporting quality of patient-reported functional and health quality outcome measures[13]. Previous trials have failed to meet these criteria. Furthermore, engagement with initiatives such as the Core Outcome Measures in Effectiveness Trials (COMET) will improve the reporting of clinical trials.

Whilst this protocol is for a feasibility study, the following main trial would address the issues raised above with well-designed methodology and reporting, adhering to these international standards.

Cost effectiveness

An NIHR Health Technology Assessment published in 2015[14] performed an extensive systematic review and economic analysis of hip replacement and concluded that they were unable to advise on the best prosthesis due to lack of evidence and poor trial quality. The appraisal called for well-designed pragmatic RCTs and data linking PROMs to implant type.

Pennington et al 2013[15] performed a cost effectiveness study comparing types of hip implant using a data set from the UK National Joint Registry and PROMs data and determined that although a fully cemented total hip arthroplasty was the cheapest option, a hybrid total hip arthroplasty was shown to be the most cost effective in terms of cost and optimal patient function. However, this study was an observational study based on single time point PROM data collection at 6 months post-surgery and using a data set which has inherent problems in terms of data reporting of revision procedures.

In this feasibility trial we will not be performing a full health economic analysis but advice has been sought from a health economist and the full trial will include a health economist co-applicant. Such analysis will use individual patient-level data on healthcare resource use and health-related quality of life as measured in the full trial. The subsequent economic analysis will take the perspective of the NHS and personal social services.

Guidance on the selection of the PROMs questionnaires that are required to ensure a sensitive and validated measure that will be able to deliver the aims of the trial has been sourced from an expert in outcomes assessment, who is a co-author of this protocol.

Types of hip replacement

A total hip arthroplasty consists of a socket which is placed in the patient's bony acetabulum, a stem which is placed into the femur and a ball which is attached to the stem and sits (articulates) within the socket to replicate the native ball and socket joint. There are many different implant companies in the UK offering a variety of different types of hip implant but they can all be broadly grouped into 3 categories.

A fully cemented total hip arthroplasty is one which relies on fixation of the socket and the stem to the bone using bone cement. The most common type is a plastic socket, a metal or ceramic ball, and a metal stem.

A fully uncemented total hip arthroplasty is one where a metal socket and stem have a particular coating or finish which allows the patient's own bone to grow into or onto the metal surface thus achieving fixation and stability. Again, a metal or ceramic ball can be utilised. A plastic or ceramic liner is placed inside the metal socket. These implants tend to be used more frequently in younger patients.

Commonly, a mixture of techniques can be utilised. A hybrid total hip arthroplasty is one where the socket is uncemented and the femur is cemented. A reverse hybrid total hip arthroplasty is where the socket is cemented and the femur is uncemented. The latter is less frequently performed.

The National Joint Registry for England, Wales and Northern Ireland[16] indicates that 27.3% of THAs are cemented, 31.2% are hybrid and 36.4% are uncemented. This clinical variation is based largely on exposure during training and philosophy of surgeons rather than being driven by evidence. A recent Health Technology Assessment has concluded that they were unable to advise on the best prosthesis due to lack of evidence and poor trial quality[14].

A recent Department of Health initiative, Getting it Right First Time[17], has been advising NHS trusts on implant choice for THA. The advice has been based on complication rates and costs and has largely been advocating the use of cemented stems. Building on this work we are therefore comparing the functional outcomes of patients randomised to receive either a fully cemented or a hybrid (cemented stem, uncemented socket) THA.

2.2 Rationale

Rationale

There have been a number of recommendations for further, high quality RCTs to be performed in this area[5, 10]. NIHR portfolio searches and trial registry searches have not identified any such studies. We therefore plan a pragmatic study comparing two common groups of implant type, to investigate the influence of implant type on patient reported functional outcomes.

When referring to hip replacement implants according to the type of fixation, the groupings include fully cemented, hybrid, reverse hybrid and fully uncemented. As indicated above, this study is comparing two common groupings of hip implants, cemented versus hybrid fixation. Together these two groups of hip replacements represent 58.5% of the hip replacements performed in the UK in 2018[16]. Whilst the fully uncemented group representation in 2018 was 36.4%, we have chosen not to include this group of hip replacements for three reasons. Firstly, the failure rates reported in the National Joint Registry for this class are higher for all age groups above 55 years (the majority of patients undergoing THA are in this group). Secondly, discussions with our potential recruiting surgeons have indicated an unwillingness to use fully uncemented THA in the older patient group (over 65s). Thirdly the 'Getting it Right First Time' report[17] (DoH initiative) is encouraging NHS trusts to move away from fully uncemented THAs due to the lower survivorship and higher treatment costs.

We acknowledge that there is a large choice of individual implants available to surgeons from many different manufacturers. It would be unrealistic to expect all NHS Trusts to use the exact same implant and manufacturer for THA and therefore a pragmatic trial comparing groups of hip replacement will generate data that is a better reflection of the real world. We hope that the outputs will therefore be relevant and more generalisable to NHS hospital Trusts and surgeons performing this type of surgery.

Prior to conducting the definitive RCT, there are feasibility questions to be addressed.

Quantitative questions:

The most important of these is to determine whether it is possible to recruit an adequate number of patients within a suitable timeframe to the study. A number of recent national orthopaedic RCTs have suffered from low recruitment rates. It is

therefore important to identify realistic recruitment rates prior to engaging upon the full study.

The primary outcome measure for the full study will be a patient-reported functional outcomes questionnaire. In order to perform accurate sample size calculations, we need to know the variability (standard deviation) and loss to follow-up rate for the proposed method of collection of these scores.

One concern with comparative surgical trials is that during surgery, the surgeon may decide to use the alternative method due to some new or unforeseen intraoperative surgical finding. This would potentially skew the trial results and the rate of this occurrence is unknown. Whilst we will analyse the functional results on an intention to treat basis, we will measure the rate of treatment cross-over during surgery. During the feasibility study, the opportunity will also be used to survey potential sites and surgeons for their willingness to be involved in a future trial and to estimate the number of patients that may be included.

Qualitative questions:

Recruitment rates can be an indicator of acceptability of a study to participants. However, they do not provide insight into reasons for declining to take part, or perceived benefits of participation. Qualitative interviews allow experiences and understandings to be explored in depth such that perceived benefits and concerns regarding taking part in research can be understood and the subsequent research can therefore be designed to take account of such concerns. Qualitative research embedded within a feasibility study can lead to specific recommendations to enhance data collection[18]. In the present project, qualitative research, involving some patients who choose to take part as well as some who decline, will identify any problems within the recruitment and research processes from a patient perspective, and also identify any concerns about being randomised to these treatments. While all patient participants in the study will receive THA, there may be concerns as to whether or not they are receiving the optimal treatment for them, or dissatisfaction about being blinded to their treatment details. It will be important to identify any concerns and to appropriately address them for a definitive trial.

To enhance the data set further, we plan to interview health professionals involved in recruiting patients and collecting data, to learn about their perceptions of barriers and facilitators to patients taking part and completing self-report measures. We anticipate this to be a particularly useful approach for gaining insights into these questions if individuals who do not wish to take part in a randomised study are reluctant to take part in research generally and so also decline taking part in an interview. Interviewing health professionals will also allow us to learn to any procedural issues around recruiting participants and collecting data for the HipHOP study.

For the trial to be feasible, surgeons are needed to participate and to refer their patients to the study for randomisation; they are unlikely to do so unless they believe that there is uncertainty about the efficacy of treatment options[19]. Qualitative interviews with surgeon participants – those at the study sites who are willing for patients to be randomised, as well as those who decline, and surgeons at other potential sites for the full trial - will enable the extent to which equipoise is perceived, and any concerns surgeons might have about taking part, to be understood.

Finally, it is expected that the definitive trial will provide guidance as to the most appropriate THA procedure. For such guidance to impact on patient and cost

outcomes, it needs to be implemented in practice, and it is unfortunately common that research findings are not implemented in practice[20]. Surgeon participants will therefore be asked for their thoughts about receiving such guidance, and what they perceive to be barriers or facilitators to following such guidance in practice.

2.3 Objectives

The aim of this research is to ascertain the feasibility of performing a RCT comparing patient-reported functional outcomes and cost effectiveness of THA using either a fully cemented or a hybrid total hip implant.

Workstream 1:
Primary

To ascertain the feasibility of performing a comparative trial of hybrid or cemented implants for total hip replacement.

Secondary
To Assess:

1. Recruitment to a trial of this nature
2. Capture rate for postal/telephone follow-up
3. Rate of trial withdrawal
4. PROMS data statistics to determine the power required for the full study
5. Intra-operative and post-operative safety
6. To identify the incidence of treatment cross over during surgery
7. To determine the feasibility of conducting a within-trial cost-utility analysis

Workstream 2:

1. To understand patient experiences of the trial and their reasons for taking part or declining to participate
2. To understand surgeons' perceptions of the trial and equipoise, to establish factors underlying their willingness or unwillingness to participate in a trial, and to understand any barriers to implementation in practice of trial findings.
3. To understand health professionals experiences of recruiting participants to the trial and data collection, to learn about their thoughts regarding patient perceptions of the study, and to identify any changes that could enhance recruitment and running of the larger study.

2.4 Potential Risks and Benefits

2.4.1 Potential Risks

The risks of total hip replacement are fully understood and discussed with patients prior to surgery as part of the consenting for surgery process. All patients within the trial and who take part in qualitative interviews would be undergoing total hip replacement surgery even if they were not entered into the trial. All patients will have been assessed as being suitable to receive either type of hip implant as part of the study eligibility criteria; therefore participation within the trial does not pose any additional risks to the patients above routine care and no steps to mitigate risks of the surgery are required.

In interviews, when discussing their experiences of surgery, the trial, and recovery, it is possible that patient participants could talk about issues they find upsetting such as worries about surgery or pain. Should any participant show signs of distress then the study distress policy will be followed.

There are no anticipated risks for surgeon or other health professional participants taking part in interviews.

2.4.2 Known potential Benefits

The potential benefits of hip replacement surgery are well known. The purpose of the study is to try and identify any possible benefits of one type of implant over the alternative. Patient participants will be confirmed by an investigator as being suitable to receive either type of implant.

There are no specific benefits of taking part in the qualitative interviews, but people sometimes find it helpful to talk about their experiences with an interested individual.

3 SELECTION OF SITES/CLINICIANS

For the purposes of clarity, use of the words 'Site', 'Centre' and 'Hospital' are interchangeable references for the locations the participants will be recruited from and will differ depending on the context in which they are used.

For Workstream 1, each participating Site (and Investigator) has been identified on the basis of:

- Having at least one lead surgeon with a specific interest in, and responsibility for, managing patients who undergo total hip arthroplasty.
- Showing enthusiasm to participate in the trial
- Ensuring that sufficient time, staff (including research nurses) and adequate facilities are available for the trial
- Providing information to all supporting staff members involved with the trial or with elements of the patient's management
- Acknowledging and agreeing to conform to the administrative and ethical requirements and responsibilities of the trial, including voluntarily agreeing to follow the relevant aspects of the Good Clinical Practice (GCP) guidelines.

For Workstream 2, participating sites have either been involved in Workstream 1 or (for some surgeons who will be interviewed) are sites that the research team have identified as possible further sites for the full, definitive trial.

3.1 Site/Clinician Inclusion Criteria

a. Organisation Information Document
b. Research Site Agreement
c. Confirmation of capacity and capability from NHS Trust
d. Receipt of evidence of the above by LCTC

3.2 Site/Clinician Exclusion Criteria

Those sites who do not fulfil the above inclusion criteria will not be permitted to participate in the trial.

4 TRIAL DESIGN

4.1 Overall Design

HipHOP is a randomised feasibility study in preparation for a phase III, two arm, blinded, multi-centre, pragmatic randomised controlled trial comparing fully cemented and hybrid total hip arthroplasty in patients undergoing total hip arthroplasty.

This feasibility study will have both quantitative and qualitative elements, referred to as Workstream 1 and Workstream 2 respectively.

The Workstream 1 population is patients undergoing a primary total hip arthroplasty. Patient participants will be recruited from three sites and randomised to the two arms of the trial to receive either a fully cemented hip implant, or a hybrid hip implant. A total of 40 patient participants will be randomised on a 1:1 ratio. Recruitment will take approximately 6 months. Patient participants will be blinded to the type of hip prosthesis received. All possible efforts will be made for the patient participants to remain blinded until their 3-6 month post-operative PROMS are completed to ensure the integrity of the outcomes reporting. Staff collecting outcome data will also be blinded where possible (see section 9).

There are no exclusions to the *size* of socket used in the procedure. Deviation from the socket *type* that is selected at random is allowed, but only if it is established during surgery that the randomised socket type is unsuitable.

Comparison of the types of implant will be made using data collected using Patient Reported Outcome Measures. A healthcare resource use survey will also be provided to patients to complete. Data from this survey will be used to determine if a cost analysis will be possible in a larger phase III study.

Participants would have reached the end of their study involvement once their 3-6 month post-operative visit has been completed.

The Workstream 2 population is patients who both accepted or declined participation in Workstream 1, consultant orthopaedic surgeons and other health professionals.

4.2 Endpoints

The intention is to investigate the rate of recruitment, plus compliance with study procedures and assessments, in patients undergoing a primary total hip arthroplasty. Additionally, patients will be interviewed to elicit their reasons for accepting or declining the invitation to participate and their experiences of trial procedures. Consultant surgeons will also be interviewed for their views on their willingness to enrol patients in a total hip arthroplasty trial and about any barriers there might be to changing their surgical practice following the results of a larger phase III trial. We will also interview health professionals who have been involved in the recruitment of patients, or who have collected patient self-reported data, for their experiences of trial procedures and patients' willingness to participate.

Primary and Secondary Endpoints, along with their measures, are described in detail in section 11.2.

WORKSTREAM 1

(Referred to as ‘Part 1’ in participant documentation)

5 STUDY POPULATION

The population is patients undergoing a primary total hip arthroplasty.

5.1 Eligibility Criteria

The HipHOP trial aims to recruit 40 patient participants based on sample size calculations described in section 11.3. All patient participants must provide written, informed consent before any study procedures occur (see Section 6 for more information regarding the informed consent processes) and must meet all eligibility as described below.

Inclusion Criteria

Potential patient participants eligible for the trial must comply with all of the following at randomisation:

1. Age 18 years and above
2. Undergoing a primary total hip arthroplasty with either a fully cemented or hybrid implant[2]
3. Able to give informed consent prior to randomisation
4. Able to communicate in both written and spoken English

Exclusion Criteria

Any patient participant meeting any of the criteria listed below prior to randomisation will be excluded from study participation:

1. Previous surgery to the hip joint.
2. All procedures with an indication other than osteoarthritis
3. Patient requiring complex total hip arthroplasty surgery, specifically augmentation of the acetabulum (e.g. structural bone graft or metal augment) and/or shortening/de-rotational osteotomy of the femur at the time of surgery.
4. Patients requiring bilateral simultaneous total hip arthroplasty
5. Vision impairment that precludes the completion of PROMS questionnaires.

5.2 Patient Participant Transfer and Withdrawal

In consenting to the trial, patient patients are consented to trial treatment, follow-up and data collection. If post-operative voluntary withdrawal occurs, the participant should be asked to allow continuation of scheduled evaluations, and be given appropriate care under medical supervision until the symptoms of any adverse event resolve or the subject's condition becomes stable.

Participants who lose capacity after providing consent and while still in follow-up will be withdrawn from the study. In these instances, data up to the point of withdrawal will still be used for analysis and the patient will not be replaced.

[2] All prostheses and bone cements that are used must be CE marked and used in accordance with their intended use. There is no limitation as to the manufacturer of prostheses used and surgeons will continue to use the implants that they are familiar with. Furthermore, surgeons will be free to use whichever head/socket material and diameter they feel appropriate. The surgical approach, anaesthetic type, rehabilitation after surgery and other concomitant factors will be as per the surgeons' normal care. These factors will be recorded.

5.2.1 Participant Transfers

Due to the low number of participating sites and their geographical difference, it is unlikely that participants relocating to another part of the country will be able to be followed-up at another hospital that is participating in HipHOP. However, every effort should be made for the participant to be followed-up at another participating site, and for this site to take over responsibility for the patient participant.

Should a transfer be possible, a copy of the participant CRFs should be provided to the new site. The patient participant will remain the responsibility of the original site until the PI at the new site has signed the Transfer CRF.

In the event of any transfer, the informed consent obtained by the original site remains valid; i.e. consent does not have to be re-obtained.

5.2.2 Withdrawal from Trial Intervention

If a patient participant who has already given consent, or their surgeon, decides the operation cannot go ahead, consented participants will be withdrawn from the study.

Patient participants who withdraw from the study in this manner, and prior to undergoing their total hip arthroplasty surgery will be replaced.

Patient participants may be withdrawn from the study for any of the following reasons:

a. Participant withdraws consent.
b. Intercurrent illness preventing surgery.
c. Pregnancy.
d. Any other change in the patient participant's condition that justifies the prevention of surgery or follow-up in the clinician's opinion.

If a participant wishes to withdraw from post-op completion of PROMS, sites should explain the importance of remaining on trial follow-up, or failing this, of allowing data from the routine six-week follow-up visit to be used for trial purposes.

5.2.3 Withdrawal from Trial Completely

The patient participant can withdraw consent at any time without providing a reason.

Patient participants who wish to withdraw consent for the trial will have pseudonymised data collected up to the point of withdrawal of consent included in the analyses.

Participants who withdraw from the trial completely will not contribute further data to the trial, unless this is required under applicable legislation (e.g. safety events) - the LCTC should be informed in writing and a withdrawal CRF should be completed.

Patient participants who have provided consent and been randomised, and whose surgeries are delayed beyond the agreed time-point for participation in the study will be withdrawn. This date will be advised to sites in advance. These participants will return to their normal clinical care pathway. They will not be replaced and follow-up data will not be collected.

6 CONSENT AND ENROLMENT

Patient participants are undergoing elective total hip arthroplasty. With the exception of the type of implant used being selected by randomisation, all surgical and medical examinations, procedures and tests are as per routine care.

Some or all of the following questionnaires require completing at different time points of the study.

- Oxford Hip Score (OHS) (https://www.ncbi.nlm.nih.gov/pubmed/10158596)
- EuroQol 5 Dimension, 5 Level Quality of Life Questionnaire (EQ-5D-5L™) (https://www.ncbi.nlm.nih.gov/pubmed/21479777)
- Self-administered Patient Satisfaction scale (SAPS) (https://www.hindawi.com/journals/arthritis/2011/591253/)
- Forgotten Joint Score (FJS) (https://www.ncbi.nlm.nih.gov/pubmed/22000572)
- Work Productivity and Activity Impairment-Specific Health Problem (WPAI-SHP) (https://www.ncbi.nlm.nih.gov/pubmed/10146874)
- Healthcare resource use survey (Bespoke to HipHOP)

6.1 Screening

A pseudonymised screening record of those patients identified a being potentially eligible to participate in Workstream 1 is to be maintained, regardless of whether they accept or decline.

The screening log will be made available via the REDCap database to sites that are open to recruitment.

6.2 Consent

Consent must be obtained before any trial specific procedures are carried out.

To assist with the approach method and consenting procedures, decision trees follow later in this section. These are for guidance only and can be flexible to complement existing procedures at the recruiting site.

Note: Consent will need to be reaffirmed if surgery does not occur within eight weeks (i.e. 56 days) of it most recently being given. The day on which consent was most recently given is day 0. Reaffirmation of consent does not require completion of an informed consent form, but is to be recorded within the patient notes.

If the patient declines the opportunity to participate, the site research team will record their reasons for refusal on the screening log. Decliners are not obliged to provide a reasons for non-participation, however efforts to elicit their reason for not participating should be made and recorded.

6.2.1 Patient's identified in clinic

Once eligibility has been confirmed, and the patient's interest in the study also confirmed by an orthopaedic surgeon named on the delegation log, an Investigator or other appropriately trained member of the research team, e.g. Health Professional or Trial Administrator, will provide the patient with a REC approved Patient Information Sheet, plus a comprehensive verbal explanation of the study before discussing the trial with the patient. Throughout the consent process, potential patient participants will be encouraged to ask questions and will be reminded that they can withdraw at any time without their clinical care being affected. If the patient is willing to participate in the trial, consent can be obtained immediately after the discussion.

6.2.2 Patient's identified from operation waiting list – with time to PIS by post

Potential patient participants that are identified from operation waiting lists will be telephoned by a member of the direct care team to ascertain their basic interest in being involved in the study. Subsequently, and if the patient is interested, their details will be passed to the research team, who will post a copy of the Patient Information Sheet, with an introductory covering letter, to them in advance of a more detailed discussion by telephone. This telephone conversation must follow the same structure as a face-to-face discussion (see previous paragraph). The obtaining of consent from these patients will be deferred until their next hospital appointment. If their next appointment happens to be their day of surgery, consent can only be obtained prior to the patient receiving general anaesthetic or other medication that may reduce their capacity to understand the purpose of the Informed Consent Form.

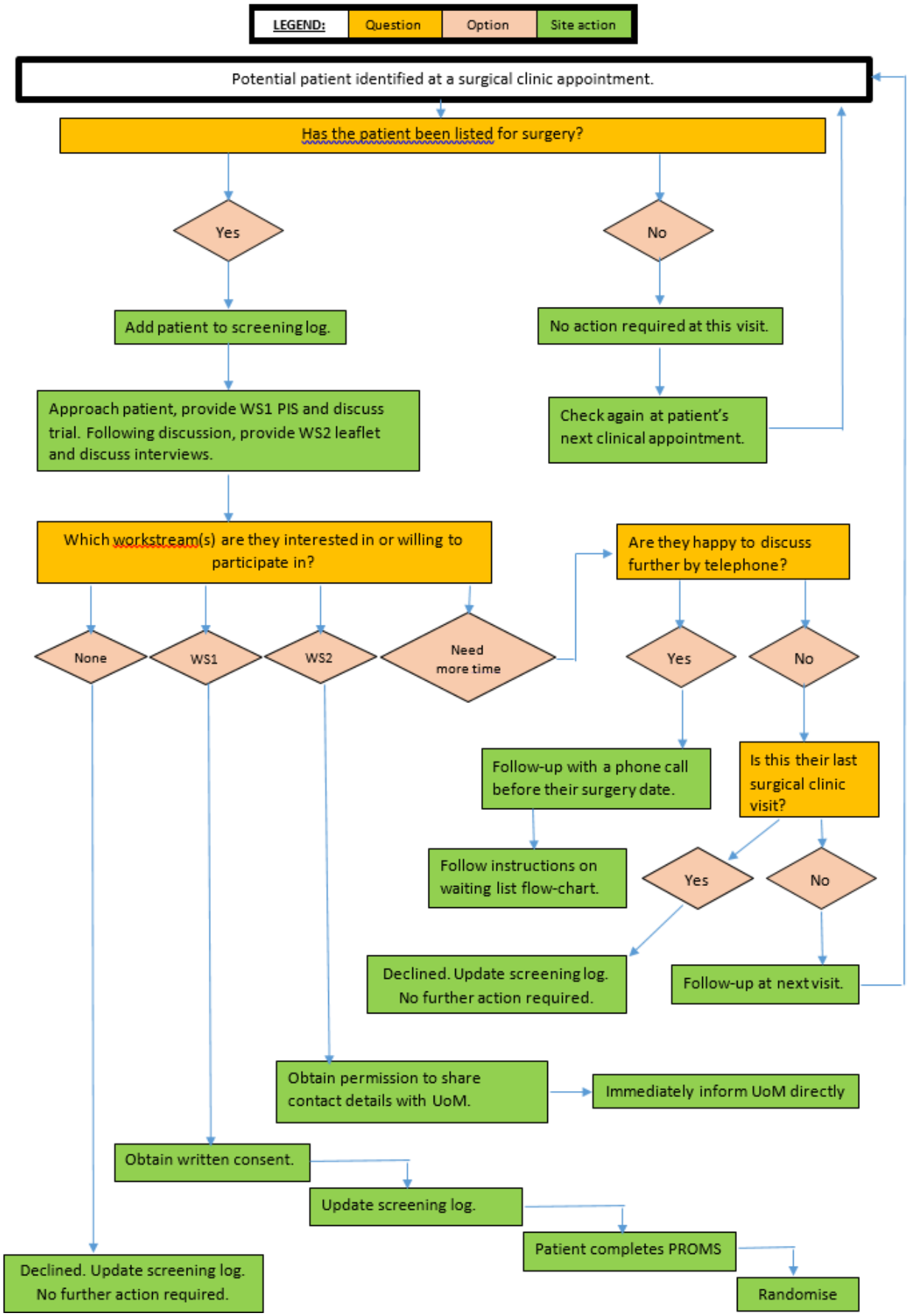
6.2.3 Patient's identified from operation waiting list – without time to PIS by post

Potential patient participants that are identified from operation waiting lists will be telephoned by a member of the direct care team to ascertain their basic interest in being involved in the study. Subsequently, and if the patient is interested, their details will be passed to the research team. As the patient's operation is imminent, it will be explained to the patient that they will be approached by a member of the research team on their day of surgery who will discuss the study in more detail with them. Consent can only be obtained prior to the patient receiving general anaesthetic or other medication that may reduce their capacity to understand the purpose of the Informed Consent Form.

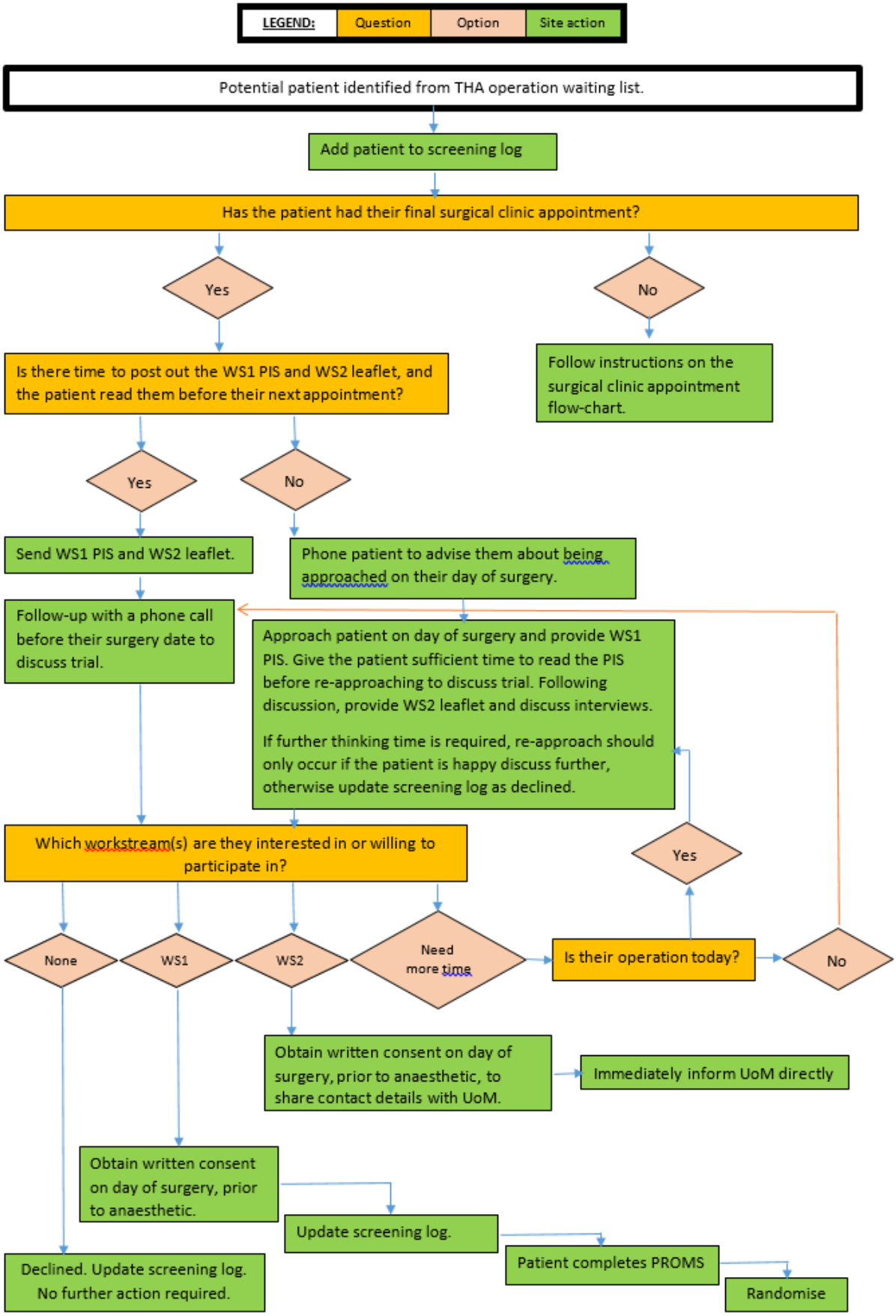
6.3 Loss of Capacity after providing consent

Should a patient lose capacity during the study they will be withdrawn from any future participation. See section 5.2 for further details.

Decision Tree 1 – Patient identified at a surgical clinic appointment



Decision Tree 2 – Patient identified from a THA operation waiting list



7 PARTICIPANT TIMELINES AND ASSESSMENTS

7.1 Co-enrolment Guidelines

Patient participants in Workstream 1 of the HipHOP trial should not be recruited to other similar studies of hip replacement surgery. Similarly, patient participants already participating in other trials of total hip replacement should not enter Workstream 1 of the HipHOP trial.

If a participant is only taking part in Workstream 2 of the HipHOP study, they can be recruited to other studies of hip replacement surgery.

Any queries should be addressed to the trial coordinator.

7.2 Screening / Baseline

These procedures can occur on separate occasions or on the same day if required.

Screening procedures involve identifying and consenting the patient participant. See section 5.1 and section 6 for further details.

Baseline procedures can be done any time after consent has been obtained but must be completed prior to the patient being randomised. If baseline procedures are not completed until the day of surgery, they must also be completed prior to the patient participant receiving surgery related anaesthetic or other associated medication that may affect their ability to complete them accurately.

Note: All baseline procedures will need to be repeated if surgery does occur within eight weeks (i.e. 56 days) of their completion. The day of completion is day 0.

PROMS questionnaires to be completed are listed below. The Oxford Hip Score is to be completed first, others are shown in a recommended order of completion of most recent recall period:

- Oxford Hip Score
- EQ-5D-5L™
- Forgotten Joint Score
- Work Productivity and Activity Impairment–Specific Health Problem
- Healthcare Resource Use Survey

7.3 Randomisation

Randomisation shall occur pre-operatively once the patient has been deemed eligible for the study, provided written informed consent and their baseline procedures completed. The randomisation sequence is pre-determined by LCTC, see section 11.1 for further details.

The randomisation will be processed using REDCap, a commercially available on-line research database system, and will be processed by the research team at the recruiting site. It should be completed as soon as possible for the purposes of operation list planning and implant procurement, and must be no later than the day prior to surgery. The only caveat to this deadline is for patients who will not be consented until the day of their surgery, in which case randomisation should be completed as soon as it is possible to do so.

7.4 Day of Surgery and In-Patient stay

Clinical data, including length of stay in hospital, changes to the type of implant used and safety data will be collected during this period. Specific information on reporting adverse events can be found in section 12.

Following the surgery, the scrub team will complete an intraoperative healthcare resource use questionnaire collating source data on length of surgery and usage of equipment and disposables during surgery etc.

7.5 6 weeks post-op

All patient participants will be reviewed in a routine outpatient clinic at 6 weeks postoperatively (from date of surgery). Please also see section 7.12 on contingency planning.

PROMS questionnaires to be completed are listed below. The Oxford Hip Score is to be completed first, others are shown in a recommended order of completion of most recent recall period:

- Oxford Hip Score
- EQ-5D-5L™
- Self-Administered Patient Satisfaction scale
- Forgotten Joint Score
- Work Productivity and Activity Impairment–Specific Health Problem

Data will also be collected Adverse Events of Special Interest; these will primarily be surgical complications, such as but not limited to returns to theatre for dislocation, fracture or wound problems; any prescriptions for antibiotics will be noted and any unanticipated contact with the surgical team or GP regarding the surgery.

The earliest this visit can occur is 3 weeks postop and the latest is 12 weeks postop from the date of surgery. Visits outside of these parameters will be recorded as protocol deviations but will not affect the patients continuing participation in the trial.

Every effort should be made to meet the patient in person during the visit. Should this not be possible the questionnaires should be posted as soon as possible to the patient for their completion. Details on how and when to return the questionnaires are included within the covering letter. (See also section 7.7 Loss to follow-up.)

7.6 3-6 month post-op

Patient participants will be required to complete their PROMS questionnaires and healthcare resource use survey between 3 and 6 months postoperatively (from date of

surgery). This follow-up period will be dictated by the remaining duration of the study. All patient participation activity is expected to be completed by the end of October 20201. See the table below.

Month of Operation	**Follow-up time point**	**Follow-up duration**
January ‘21	July ‘21	6 months
February ‘21	August ‘21	6 months
March ‘21	September ‘21	6 months
April ‘21	October ‘21	6 months
May ‘21	October ‘21	5 months
June ‘21	October ‘21	4 months
July ‘21	October ‘21	3 months

PROMS questionnaires and a healthcare resource use survey will be sent in the post for the patient participant to complete. The accompanying cover letter will advise that the Oxford Hip Score is to be completed first, others are shown in a recommended order of completion of most recent recall period:

- Oxford Hip Score
- EQ-5D-5L™
- Self-Administered Patient Satisfaction scale
- Forgotten Joint Score
- Work Productivity and Activity Impairment–Specific Health Problem
- Healthcare Resource Use Survey

A member of the hospital research team will contact the patient participants by phone before distribution to inform them of the upcoming postal questionnaires. The questionnaires should be posted early enough that the patient participant is in possession of them at the required 3-6 month post-operative date.

Patient participants will also be asked about any return to theatre required and any unanticipated contact with the surgical team or GP regarding the surgery.

The earliest that this data can be collected is 4 months postoperatively and the latest time is 8 months. Completion of these questionnaires outside of these parameters will be recorded as protocol deviations but will not affect the patients continuing participation in the trial.

Details on how and when to return the questionnaires are included within the covering letter.

7.7 Loss to follow-up

If after posting the questionnaires to the patient their return is not forthcoming, two reminder telephone calls should be made to them. If these calls prove unsuccessful, a reminder letter should be sent.

The timing of the reminder calls and letter is at the discretion of the treating hospital, however a suitable time-frame should be implemented and care should be taken in the timing of the final reminder letter so it allows sufficient time for the completion of the questionnaires within the stipulated +/- allowance for the post-op time point.

If no reply is received after the letter has been posted and sufficient time allowed for completion and return of the questionnaires, the patient shall be classed as lost to follow-up and the relevant CRF completed and provided to LCTC.

7.8 Schedule of trial procedures

Table B below describes Workstream 1 procedures and their time-points.

Table B: Trial procedures

	TIMEPOINT					
PROCEDURE	Screening	Baseline	Randomisation	Day of surgery	Routine 6 weeks Post-op (-3 weeks / +6 weeks)	3-6 months Post-op (-2 month / +2 months^)
Identify eligible patient from records	X					
Approach patient and discuss trial	X					
Obtain Consent	X					
Randomise patient			X			
Demographics	X					
PROMS – Oxford Hip Score		X			X	X
PROMS – EQ-5D-5L™		X			X	X
PROMS – Self-Administered Patient Satisfaction Scale					X	X
PROMS – Forgotten Joint Score		X			X	X
PROMS – Work Productivity and Activity Impairment–Specific Health Problem		X			X	X
Healthcare Resource Use Survey		X				X
Data collection on routine surgery				X		
Report Serious Adverse Events or Incidents				X	X	X

^Yet no later than October 2021

7.9 Procedures for assessing Efficacy

Clinicians will use their usual criteria to determine if an intervention is deemed to have failed clinically and if a re-intervention is necessary. This information will be recorded in the patient participant's notes and on the appropriate CRF. The nature of any re-intervention will be at the discretion of the treating clinician who will use their skill, knowledge and expertise to determine the most appropriate treatment.

7.10 Procedures for Assessing Safety

Safety will be assessed through reporting on post-operative Adverse Events as described in section 12.

7.11 Quality of Life and Health Economics

Health Related Quality of Life and Health Economics outcomes measures
Health-related quality-of-life (HRQL) and other outcomes for use in the health economics component of the study will be assessed using the following questionnaires:

- Oxford Hip Score (OHS)
- EuroQol 5 Dimension, 5 Level Quality of Life Questionnaire (EQ-5D-5L™)
- Self-administered Patient Satisfaction scale (SAPS)
- Forgotten Joint Score (FJS)
- Work Productivity and Activity Impairment–Specific Health Problem (WPAI-SHP)
- Healthcare Resource Use Survey

Baseline data will be collected prior to the patient participant being randomised, with further collections at 6 weeks and 3-6 months post-operation. The only exclusions to this are the Health Resource Use Survey data, which is only collected at baseline and 3-6 months post-operation and SAPS data, which is not collected at baseline and will only be collected at 6 weeks and 3-6 months post-operation.

- The Oxford Hip Score© is used to assess joint-specific pain and functional limitations encountered by the patient participant in day-to-day activities over the preceding 4 weeks.
- EQ-5D-5L™ is a preference-based HRQL measure comprising five domains, each with five levels. HRQL scores can be attached to each of the possible 3125 health states it describes.
- Self-administered Patient Satisfaction scale is a tool to measure patient satisfaction with their operation, pain, and ability to do daily activities and recreational activities.
- The Forgotten Joint Score is a 12 question scale used to measure joint awareness. It has been extensively validated to assess outcomes after total hip arthroplasty.
- Work Productivity and Activity Impairment-Specific Health Problem records data on work time and productivity over the preceding 7 days.
- The Healthcare Resource Use Survey is a HipHOP specific questionnaire

7.12 Contingency planning

In the event of national emergency (e.g. COVID-19) which prevents patients attending routine hospital appointments, the following amendments to practice will be followed:

- Any suspension of recruitment will be based on national guidance regarding elective surgeries, i.e. recruitment will be suspended temporarily if elective surgeries are postponed.
- If routine post-operative clinic appointments are postponed, PROMS for completion at 6-weeks post-op will be posted to the patients for their completion at home.

8 TRIAL CLOSURE

8.1.1 Closure to recruitment

Investigators will be informed when patient participant recruitment is to cease.

Trial enrolment may be stopped at a site when the total number of participants for the trial has been obtained.

The trial will close to recruitment once all Workstream 1 patient participants have been randomised and all Workstream 2 patient, surgeon and other health professional participants have completed their interviews. These closures may not necessarily occur simultaneously.

8.1.2 Trial closure

The end of the trial is defined to be the date on which data for all participants are frozen and data entry privileges are withdrawn from the trial database. The trial may be closed prematurely by the Trial Steering Committee (TSC).

Site and closure activities will be centrally coordinated and conducted in accordance with LCTC processes regardless of whether the trial closes as planned or prematurely. This includes activities such as:

- End of Trial notification to REC
- Trial-related materials reconciled and returned/disposed of as appropriate
- All site data entered onto the study database, discrepancies raised and satisfactory responses received
- Quality Control checks of the Investigator Site Files, Pharmacy Files and Trial Master File as appropriate.

9 BLINDING

To prevent bias in the completion of their answers to PROMS questionnaires, it is key that for the duration of their time on the study, i.e. until the 3-6 month post-operative PROMS questionnaires have been completed, a patient participant remains blinded to the type of implant they have received.

It is acknowledged that it is impossible to blind the surgeon, operation team and other healthcare professionals to the type of implant the patient participant received. Members of the research team being aware of the implant type will have no bearing on the outcomes of the study, however every effort must be made to ensure that patient participants remain blinded to the type of implant they received, at least until a patient has completed their 3-6 months post-operation PROMS questionnaires. These efforts must include, but are not limited to:

- Excluding members of the research team from correspondence that reveals the randomised allocation of the type of implant.
- Ensuring the patient is provided with and wears ear plugs during surgery. Alternatively, they can provide their own device and earphones to listen to music etc. instead (earphones do not have to be to any particular standard or specification, e.g. 'noise cancelling').
- Ensuring post-operative documentation that the patient or research team may have access to (e.g. discharge letter, physiotherapy referral) do not refer to the type of implant used.
- Marking/Annotating the operation notes to advise the reader to not disclose or allude to the type of implant used when in communication with the patient or research team.

If a patient participant does accidentally becomes unblinded to the type of implant they have received, the relevant CRF will need to be completed and returned to LCTC. Such occurrences will be recorded as protocol deviations but will not affect the patient continuing participation in the trial. Corrective and preventative actions must be undertaken locally to prevent similar events leading to unblinding to other patients.

If a member of the research team accidentally becomes unblinded to the type of implant patient receives, it does not have to be reported to LCTC. Corrective and preventative actions must however be undertaken locally to prevent the patient becoming aware, e.g. remove/reduce interaction between the member of the research team and the patient participant if possible.

10 HEALTH ECONOMICS

10.1 Introduction

Economic evaluations alongside randomised control trials (RCTs) are important to inform the cost-effectiveness of the healthcare intervention being evaluated. The purpose of a feasibility study is to inform the design of a larger RCT, therefore the main focus of the health economic analysis will be to critique the performance of data collection methods used to identify and measure costs and outcomes required to conduct a full economic evaluation.

10.2 Outcomes

The National Institute for Health and Care Excellence (NICE) recommends economic evaluations apply cost-utility analysis (CUA) to assess the costs and consequences of healthcare interventions[21]. In a CUA, quality-adjusted life years (QALYs) are used as the primary outcome which capture the quality and quantity of life in a single measure. A QALY is calculated by multiplying the quality of life by the quantity of life. The quantity of life is measured using a count of the number of life years. Quality is measured using preference-weighted surveys such as the EuroQol 5 Dimensions 5 levels (EQ-5D-5L™)[22]. The EQ-5D-5L™ provides a simple descriptive profile and a single index value for health status with an associated utility tariff. Utility values will be calculated for participants and will be used to estimate Quality Adjusted Life Years (QALYs) as a measure of health benefit[22]. Total QALYs will be estimated as follows:

$$QALY = \Sigma[(U_i + U_i + 1)/2] \times (t_i + 1 - t_i)$$

Here, U = utility value and t = time between assessments. The time between assessments is the time from baseline data collection to follow-up, i.e. 3-6 months. Patients will be asked to complete the EQ-5D-5L™ survey at baseline and between three and six months follow-up.

10.3 Costs

It is understood that the fully cemented total hip arthroplasty is less expensive than the hybrid total hip arthroplasty; this may prove to be a key determinant in the cost-effectiveness of each hip replacement procedure. At present, the NHS tariff, which lists the price paid to hospital for performing certain procedures, groups both hip interventions under the same tariff (price). However, to capture the variation in the costs, the cost of each hip replacement procedures will be collected from Wrightington, Wigan and Leigh Teaching Hospitals NHS Foundation Trust procurement department and used in the analysis.

10.4 Healthcare Resource use

NICE recommend economic evaluations adopt a healthcare system perspective, therefore only those costs that impact the healthcare sector should be considered[21] and is also in line with a recently published cost-effectiveness analysis of alternative

prosthetic implants for total hip replacements[23]. A bespoke healthcare resource use survey has been designed to ask patients to self-report their use of healthcare services and resources at baseline (for the previous 6 months) and then again at 3-6 months follow-up. The questionnaire asks patients to consider their use of the following NHS services and/or resources: inpatient stay, outpatient appointment, one-day appointment, accident and emergency services, primary care, community-based services including occupational therapists, and medications prescribed.

These data will be combined with those collected by the scrub team on the day of surgery.

10.5 Analysis

A descriptive analysis of the costs and outcomes data will be completed focusing on the extent to which:

1. The EQ-5D-5L™ is able to adequately capture differences in health status before and after the hip replacement procedure and across both treatment arms of the study;
2. The resource use survey is able to record data necessary to enable a full cost-effectiveness analysis of the two hip interventions;
3. The follow-up periods specified are correct to capture changes in health status and healthcare resource use; and
4. There is a pattern or random missing data for both the EQ-5D-5L™ and resource-use survey to assess responses, sensitivity, and patterns within the missing data; particularly for resource-use surveys where missing data is a common issue.

Descriptive statistics will also report baseline patient characteristics, retention of participants and return rates for the EQ-5D-5L™ and healthcare resource use surveys. A within-trial analysis will also be conducted to estimate an indicative cost per QALY for each hip replacement intervention. The base-case analysis will use the NHS tariff for each hip replacement intervention. However, in the knowledge that the hip replacement procedures do not cost the same amount, a secondary analysis will be conducted to estimate an indicative cost per QALY using the differential costs for each hip replacement.

Given this is a feasibility study, it must be emphasised that the cost per QALY results from this analysis serve as an indication of the potential cost-effectiveness of the hip replacement procedures. The results will not provide definitive evidence on the cost-effectiveness of the interventions.

11 STATISTICAL CONSIDERATIONS

11.1 Method of Randomisation

Once consent has been obtained, participants shall be randomised on a 1:1 basis including the participating site as a stratification factor. Randomisation lists shall be produced by the trial statistician at the LCTC using randomly permuted blocks with separate lists created for each stratification factor. Lists shall be created using Stata (version 15 or above) using the add-on package 'ralloc'.

11.2 Outcome Measures

11.2.1 Primary

1. Recruitment rate will be measured by the:
    i. Total number of patient participants randomised per month, and
    ii. Ratio of successful recruitment to eligible patients approached.

11.2.2 Secondary

1. Adherence to the protocol will be measured by:
    i. the number of minor (e.g. visit time-point violation) or major (e.g. violation of inclusion criteria) protocol deviations collected on a patient participant and site level. (The definitions of minor and major protocol deviations will be in accordance with LCTC categorisations that will be allocated to each deviation by the CI after assessment of the details)
    ii. the percentage of patients in each arm that were accidentally unblinded

2. Trial withdrawal rate at 6 weeks and 3-6 months will be measured using the total number of patients randomised in the study. In addition, withdrawal rates will be presented by trial withdrawal reasons and withdrawal stage for both arms.

3. Patient participant population characteristics will be measured by collecting the following information:
    i. Age
    ii. BMI
    iii. Proportion of missing data
    iv. Loss to follow up

4. Clinical and patient reported data will be measured by collecting the following information:
    i. Patient participant-reported outcomes including change in OHS, FJS, WPAI-SHP, SAPS score and quality of life measured using the EQ-5D-5L™ at 6 weeks and 3-6 months
    ii. Revision rate, defined as the number of patient participants needing Revision arthroplasty within 3-6 months of surgery
    iii. Infection rate, measured as the rate of re-operation for infection within 3-6 months of surgery
    iv. Length of stay, measured in hours
    v. Operation time, measured in minutes

vi. Incidence of treatment cross over during surgery
vii. Incidence of intra-operative surgical complications, the proportion of patient participants experiencing greater than grade III severity will be measured and reported according to Clavien Dindo classification system[24].
viii. Incidence of postoperative surgical complications, the proportion of patient participants experiencing greater than grade III severity will be measured and reported according to Clavien Dindo classification system[24].

5. Completeness of the EQ-5D-5L™ and Healthcare Resource Use Survey will be measured by using the follow methods:
   i. Descriptive statistics will be used to assess the frequency of missing data for the EQ-5D-5L™ and Healthcare Resource Use Survey.
   ii. Any patterns in missing data will be identified through the use of descriptive statistics

11.3 Sample Size

As this is a feasibility study, no formal sample size calculation based on observing a clinically relevant difference will be obtained. A sample size target of 40 patients (with at least 2 surgeons having 6 or more patients) will enable us to estimate of variance at a surgeon and patient level variability to facilitate sample size calculation of a future study.

Based on current recruitment information we propose a recruitment period of up to 6 months. Using three recruiting sites (yielding 40 recruited patient participants by 6 months) this corresponds to a recruitment rate of 2.22 patient participants per site per month considering that sites will be opened within the first two months.

In order to better inform sample size calculations for the future study, the standard error along with 95% confidence intervals of the variance estimate for change at 6 weeks and 3-6 months of the retention rate and each of the PROMs investigated (OHS, FJS, SAPS and WPAI-SHP), along with the visual analogue scale from EQ-5D-5L™ is going to be reported from a single longitudinal model of all data. In addition, Inter class correlation (ICC) within hospitals for the PROM data will also be estimated which will also inform the sample size calculation for the future full study.

11.4 Interim Monitoring and Analyses

No formal interim analysis will be performed during the course of the feasibility study. The TSC will assess the actual recruitment rates and makes decisions on whether to stop the trial based on poor recruitment.

11.5 Analysis Plan

Feasibility and overall recruitment rate will be assessed at the opened sites by calculating the total number of patient participants randomised per month and the ratio of successful recruitment to eligible patients approached. Furthermore, observed recruitment rates, by site and overall, will be summarised along with a 95% confidence interval.

Much of the analysis will be performed using summary statistics and graphics. No formal assessments of efficacy, cost or safety across treatment arms will be made. All presentations of the data will take the form of summary analysis and graphical representations. Continuous data shall be presented using measure of median (interquartile ranges), whereas categorical data shall be presented in terms of frequencies of counts and associated percentages.

Primary and secondary outcomes will be compared between the two arms using a chi-squared or Fisher's exact test.

All analyses shall be carried out on an intention to treat basis, retaining all patient participants in their initially randomised groups irrespective of any protocol deviations. The exception to this is the analysis of safety data which shall be analysed on the safety set which is defined by the type of arthroplasty that patients receive.

Feasibility of the study will be measured on the ability of the study to meet the recruitment targets and Stop/go criteria are defined on this basis.

Following 6 months of active recruitment, a target of 40 patient participants is set. If recruitment is ≥ 80% of this target (≥32 patients) a future full study can be considered feasible. If the observed recruitment rate is between 50% and 80% of the target (20 - 31 patients) then a future full study could potentially go ahead only if satisfactory measures can be taken to improve recruitment. Such measures must be realistic and have support of the study sponsor. If recruitment is less than 50% of the anticipated rate (≤19 patients) than the study won't be considered feasible to evolve into a full one in the future.

In addition, in order for the study to be considered feasible, it should not demonstrate any serious issues related to randomisation process, patient participant retention and/or protocol deviations.

Statistical analyses will be performed using a suitable recognised statistical software such as Stata v15 or above, R v3.3.0 or above and SAS v9.3 or above.

A separate analysis plan including the above details and a shells document containing dummy figures and table shells will be provided before the final analysis.

12 SAFETY REPORTING

12.1 Terms and Definitions

Collectively, the terms and definitions below are referred to as 'safety events'.

Adverse Event (AE)
Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons whether or not related to a medicinal product or medical device.

Adverse Event of Special Interest (AESI)
An AE thought to be potentially associated with the medical product or medical device under study.

Related Adverse Event (Related AE)
An AE with a relatedness assessment of either "possible", "probable" or "causal relationship".

Adverse Device Effect (ADE)
An AE which is a result of:

- insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device, or
- a use error or intentional abnormal use of the device.

Unanticipated Adverse Device Effect (UADE)
An ADE which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report / "Instructions for Use" / protocol (i.e. considered "unexpected").

Serious Adverse Event (SAE)
An AE which meets the definition of 'serious'.

Related Serious Adverse Event (Related SAE)
A Related AE which meets the definition of 'serious'.

Serious Adverse Device Effect (SADE)
An ADE which meets the definition of 'serious'.

Unanticipated Serious Adverse Device Effect (USADE)
An ADE which meets the definition of 'serious'.

Device Deficiency
An inadequacy of an investigational medical device related to its identity, quality, durability, reliability, safety or performance, such as malfunction, use error or inadequacy in the information supplied by the manufacturer.

Adverse Incident (AI)
An event that causes, or has the potential to cause unexpected or unwanted effects involving the safety of device users (including patients) or other persons.

12.2 Responsibilities – Investigator

The Investigator is responsible for reporting safety events to LCTC in accordance with section 12.3.

12.3 Reporting requirements

Not all of the safety events listed in section 12.1 are reportable to LCTC

The safety profile of cemented and uncemented hip implants, and bone cements that are CE marked are very well known. It is therefore highly unlikely that this trial will reveal any new safety information relating to total hip arthroplasty. The recording of only Adverse Events of Special Interest, and Serious Adverse Events that are related to the device or procedure will not affect the safety of participants or the aims of the trial.

The following are reportable to LCTC:

- Any Adverse Event of Special Interest (AESI) with a severity grading of 3 or above according to the Clavien Dindo classification system[24] (see table D).
- Any Adverse Device Event that meets the definition of serious (see section 12.5) and is assessed as being related a device (i.e. an implant or bone cement).

No other safety events are required to be reported to LCTC. All safety events (regardless of the requirement to report to LCTC) are to also be recorded and reported as per local policy.

Reporting requirements decision tree:

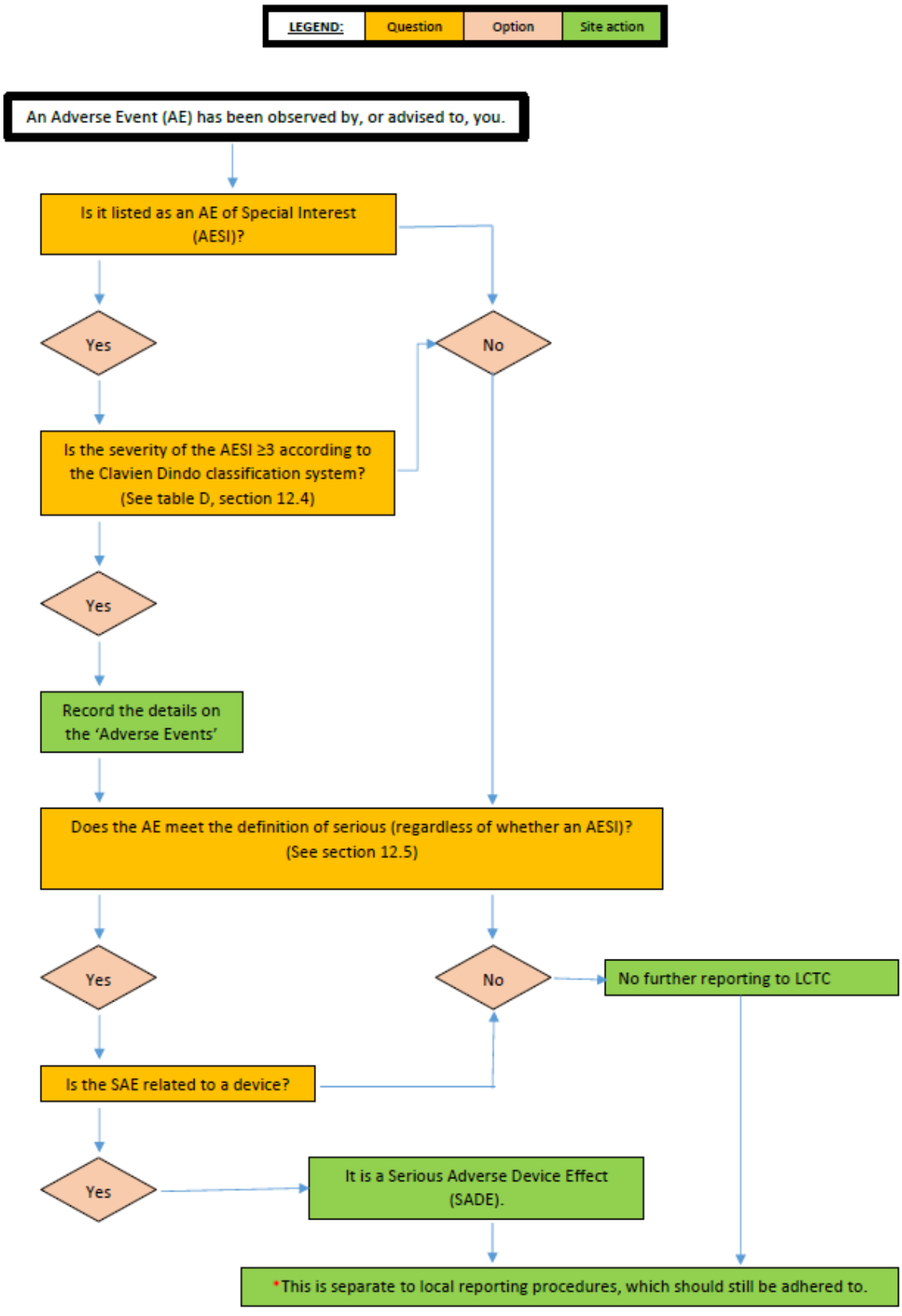


Table C: Adverse Events of Special Interest (in alphabetical order).

Event
1. Cerebrovascular accident
2. Deep infection
3. Deep Vein Thrombosis
4. Dislocation of hip (subluxation or dislocation of joint)
5. Fracture around joint including femoral shaft perforation or fracture, calcar fracture, trochanteric fracture, acetabular (fracture or perforation) or pelvic fracture (intraoperative)
6. Fracture around joint including trochanteric avulsion, femoral or acetabular or pelvic fracture (postoperative)
7. Haematoma
8. Heterotopic ossification of joint leading to pain or stiffness (periarticular calcification or ossification)
9. Loosening of implants (early or late, change in position of implants, subsidence of implants or tissue reaction/osteolysis)
10. Myocardial infarction
11. Nerve injury (temporary or permanent nerve damage including femoral, obturator, peroneal, sciatic)
12. Organ/Multiorgan failure
13. Pain from joint
14. Pneumonia
15. Pulmonary Embolism
16. Revision surgery
17. Superficial infection
18. Vascular injury (including iliac, obturator and femoral artery injury)
19. Wear or fracture or fatigue fracture of implants

12.4 Assessment of Severity

Important Note: A distinction is drawn between **severe** and **serious**. Severity is a measure of intensity, whereas seriousness is defined using the criteria in Section 12.5. However, any AE's with a severity grading of 4 or 5, according to the Clavien Dindo classification system[24] (i.e. life-threatening or fatal), also meet the criteria of serious.

Table D: Clavien Dindo classification system[24].

Grade	Definition
1	• Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions. • Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics and electrolytes and physiotherapy. • This grade also includes wound infections opened at the bedside.
2	• Requiring pharmacological treatment with drugs other than such allowed for grade 1 complications. • Blood transfusions and total parental nutrition are also included.
3a	• Requiring surgical, endoscopic or radiological intervention – not under general anaesthesia.
3b	• Requiring surgical, endoscopic or radiological intervention – under general anaesthesia.
4a	• Life-threatening complication (including CNS complications*) requiring intermediate care or intensive care management – single-organ dysfunction (including dialysis).
4b	• Life-threatening complication (including CNS complications*) requiring intermediate care or intensive care management – multi-organ dysfunction.
5	• Death of a patient.
*brain haemorrhage, ischemic stroke, subarachnoidal bleeding, but excluding transient ischemic attacks.	

12.5 Assessment of Seriousness

Important Note: The assessment of seriousness of safety events should be performed by an appropriately delegated, medically qualified member of the site research team.

An AE is termed "serious" if it:

- Led to a death, injury or permanent impairment to a body structure or a body function;
- Led to a serious deterioration in health of the subject, that either resulted in:
    - a life-threatening illness or injury, or

- a permanent impairment of a body structure or a body function, or
- in-patient hospitalisation or prolongation of existing hospitalisation (N.B. Planned hospitalisation for pre-existing condition, or a procedure required by the Clinical Investigation Plan, without a serious deterioration in health, is not considered a serious adverse event), or
- Medical or surgical intervention to prevent life threatening illness;

- Led to foetal distress, foetal death or a congenital abnormality or birth defect.

Note: the reporting of pregnancy as an SAE is not required.

12.6 Assessment of Relationship to Trial Devices or Procedure

An SAE is termed "related" if it is assessed as being 'related' to the device or procedure if it has a 'possible', 'probable' or 'causal' relationship (highlighted in green within table E below). If assessed as related (to a device or the procedure) it is classified as a Serious Adverse Device Effect (SADE). All SADEs require expedited reporting to LCTC.

The assignment of the relatedness should be made by an investigator with the delegated responsibility of assessing safety events.

Relatedness should only be assigned to the following:

a. Implant stem
b. Implant socket
c. Bone cement

If any doubt about the relatedness exists, the local investigator should inform the LCTC who will notify the Chief Investigator.

In the case of discrepant views on relatedness between the treating investigator and others, the opinion of the treating investigator will never be downgraded and the MHRA/REC will be informed of both points of view.

Table E: Definitions of Relationship

Relationship	Definition
Not related	Relationship to the device or procedures can be excluded when: • the event is not a known side effect of the product category the device belongs to or of similar devices and procedures; • the event has no temporal relationship with the use of the investigational device or the procedures; • the event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible; • the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible - and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the event; • the event involves a body-site or an organ not expected to be affected by the device or procedure;

	• the event can be attributed to another cause (e.g. an underlying or concurrent illness / clinical condition, an effect of another device, drug, treatment or other risk factors); • the event does not depend on a false result given by the investigational device used for diagnosis, when applicable; • harms to the subject are not clearly due to use error; In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the event.
Unlikely	Relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.
Possible	Relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/clinical condition or/and an effect of another device, drug or treatment). Cases where relatedness cannot be assessed or no information has been obtained should also be classified as possible.
Probable	Relationship with the use of the investigational device seems relevant and/or the event cannot reasonably be explained by another cause, but additional information may be obtained.

Causal Relationship	Event is associated with the investigational device or with procedures beyond reasonable doubt when:
	
	• the event is a known side effect of the product category the device belongs to or of similar devices and procedures;
	• the event has a temporal relationship with investigational device use/application or procedures;
	• the event involves a body-site or organ that
	  ○ the investigational device or procedures are applied to;
	  ○ the investigational device or procedures have an effect on;
	• the event follows a known response pattern to the medical device (if the response pattern is previously known);
	• the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the event (when clinically feasible);
	• other possible causes (e.g. an underlying or concurrent illness / clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out;
	• harm to the subject is due to error in use;
	• the event depends on a false result given by the investigational device used for diagnosis, when applicable.

12.7 Recording of safety events

12.7.1 Recording in patient's notes

Safety events will be identified through enquiries at study time points, including routine tests and examinations and through any emergency admissions. The patient participant will be given a card with trial details and contacts in order that any emergency admissions can be reported to the research team at their registered hospital.

The following events are to always be recorded in the patient notes:

- Any Adverse Event of Special Interest that has a severity grading of 3 or above according to the Clavien Dindo classification system[24]
- Any Adverse Event that meets the definition of serious
- All Adverse Events that would be normally be recorded as part of routine care

12.7.2 Reporting period

The period for the reporting of Safety Events ranges from the start of the total hip arthroplasty operation (i.e. knife to skin) until the patient's participation in the study is complete.

12.8 Reporting of Safety Events – Overview

Full details on the reporting of Safety Events is available within the Safety Plan and should be followed. The information below is an overview only.

12.8.1 Adverse Events of Special Interest

Any AESI with a severity grade of 3 or higher is to be recorded on the Adverse Events CRF.

12.8.2 Serious Adverse Device Events

Any SADE must be reported to LCTC on a SADE report form.

All initial and follow-up SADE reporting must be made as soon as possible and **definitely within 5 calendar days** of the site becoming aware of it.

SADE report forms are available from the LCTC portal at www.LCTC.org.uk.

There is a minimum dataset requirement within these forms to allow the relatedness assessment to be conducted; these data must be provided.

The SADE report form must be completed by an appropriately authorised and delegated member of the research team; the assessment of 'seriousness' and 'relatedness' must be performed by an appropriately medically qualified and delegated person.

Send reports to lctcsafe@liverpool.ac.uk as a secure email (i.e. '[SECURE]' must be the first word of the subject line, written in capital letters, and surrounded by [square] brackets).

If no acknowledgement of receipt is received within 2 hours please inform the HipHOP team by telephone.

(LCTC will report all Unanticipated SADEs to REC, Sponsor and MHRA; this is in addition to any local reporting policy. Reporting to MHRA will be via the Yellow Card scheme.)

12.8.3 Timeframe categories

- Intra-operative: AE occurred between the start and end of the total hip arthroplasty operation, i.e. knife to skin, to when the application of the dressing is completed.
- Early post-op: AE occurred any time after the end of the total hip arthroplasty operation, up to and including 6-weeks post-operation (i.e. 42 days, with the day of the operation being day 0).
- Late post-op: AE occurred any time in or after the seventh week post-operation (i.e. from and including day 43, with the day of the operation being day 0).

12.8.4 Follow-up of safety events

All AESIs that are reportable, and all SADEs, should be followed-up until the patient participant completes their participation on the trial, until satisfactory resolution, or until the investigator responsible for the care of the patient participant deems them stable or the event chronic (i.e. resolved with sequelae), whichever occurs soonest.

12.9 Quarantine, Labelling & Storage of Devices Involved in Safety Events

Medical devices that have been involved in an unexpected and related Safety Event, whether serious or not, should be quarantined as per local trust policy. The exception to this is for Unanticipated Serious Adverse Device Effects (USADE).

Devices involved in the USADE should not be discarded, repaired or returned to the manufacturer until the MHRA has been given the opportunity to carry out an investigation. All material evidence, i.e. devices/parts removed, replaced or withdrawn from use following an incident, instructions for use, records of use, repair and maintenance records, packaging materials, or other means of batch identification must be:

- Clearly identified and labelled;
- Stored securely.

Evidence should not be interfered with in any way except for safety reasons or to prevent its loss. Where appropriate, a record should be made of all readings, settings and positions, together with any photographic evidence and eyewitness reports.

If it is thought that an urgent examination of the device (and/or related items) may be required, upon notification of the incident an MHRA device specialist will decide whether to inspect the item urgently on site (or at other appropriate facilities), or may request that the device is sent to the MHRA. If required, the MHRA will contact the manufacturer and, if accompanied by an appropriate person, they may be allowed to inspect the items. To facilitate an investigation, it may be

possible to provide the manufacturer with a sample of unused stock from a large batch. However, until advised to the contrary by the MHRA, the manufacturer must not be allowed to exchange, interfere with, or remove any part of the product implicated in the incident as this might prejudice MHRA investigations, or those of other official bodies.

12.10 Responsibilities – LCTC

The LCTC is undertaking safety reporting duties delegated by the trial sponsor.

It is the responsibility of LCTC to report Unanticipated Serious Adverse Device Effects to REC and Sponsor, and to MHRA. Reporting to MHRA will be via the Yellow Card Scheme.

Observations of the following Safety Events will be reported to the sponsor and REC in an expedited fashion:

- Any significant difference in quantity of SADEs by implant type that are judged to be clinically important.
- Any recommendations of oversight committees, where relevant for the safety of the subjects.

Staff at the LCTC will liaise with the Chief Investigator or designated Clinical Coordinator who will evaluate the expectedness of all SADE reports received.

The LCTC will send an annual safety report containing a list of all Serious Safety Events to REC.

12.11 Assessment of Expectedness

The Chief Investigator or a Clinical Coordinator for the HipHOP trial is responsible for determining whether a SADE is expected, or not. Neither the Chief Investigator nor a Clinical Coordinator will assess expectedness for their own patient participants.

A SADE will be considered unexpected if it is not listed within the current and approved 'Instructions for Use' for the study at the time of the onset. These documents are the Reference Safety Information. See section 12.12.

The timing of the SADE in relation to the total hip arthroplasty operation should be considered where such a breakdown is provided – if this is not consistent with that described for the type of event in the Reference Safety Information the event should be considered as unanticipated.

12.12 Reference Safety Information

The documents to be used as Reference Safety Information for the assessment of expectedness for HipHOP is as follows:

- **Femoral stem:** 'Adverse Events and Complications' section of DePuy Synthes 'Femoral Hip Stem' Instruction for Use, reference IFU-78410023

- **Cemented socket:** 'Indications and Contraindications' section of DePuy Synthes Instruction for Use, reference IFU-78412358
- **Uncemented socket:** 'Adverse Events and Complications' section of DePuy Synthes 'Total Hip Prosthesis, Self-Centering™ Hip Prosthesis and hemi-hip prosthesis' Instruction for Use, reference IFU-0902-00-701
- **Bone cement:** 'Adverse Events' section of DePuy Synthes 'Unmedicated Bone Cements' Instruction Leaflet, reference IFU-0630131

Instruction for Use documents that are used as Reference Safety Information will be checked for updates prior to the first patient participant being randomised. Due to the short duration of this trial, no further checks for updates will be made and those that are in effect at that time will be used for the duration of the study

Reference Safety Information documentation will be available to the Chief Investigator and Clinical Coordinators via the LCTC portal at www.LCTC.org.uk.

13 REGULATORY AND ETHICAL CONSIDERATIONS

13.1 Ethical Considerations

Ethical review of the study is a requirement to safeguard the rights, dignity and welfare of people participating in research. Amendments made to the study after a favourable ethical opinion will be submitted and approved prior to implementation. The requirement for ethical approval applies to all participating countries.

Each participating Principal Investigator will be named on the original ethics application form or on a subsequent amendment.

13.2 Ethical Approval

The trial protocol will receive a favourable opinion of a Research Ethics Committee prior to being distributed to sites.

A copy of all site approval documents and copies of the Participant Information Sheets and Informed Consent Forms containing site logo, contact details etc. should be forwarded to LCTC before participants are approached.

13.3 Informed Consent Process

Informed consent is a process initiated prior to an individual agreeing to participate in a trial and continues throughout the individual's participation. Informed consent is required for all individuals participating in LCTC coordinated trials. In obtaining and documenting informed consent, the investigator should comply with applicable regulatory requirements and should adhere to ethical and GCP principles that have their origin in the Declaration of Helsinki.

Discussion of objectives, risks and inconveniences of the trial and the conditions under which it is to be conducted are to be provided to participants by staff with appropriate experience.

Appropriate Participant Information Sheet(s) and Informed Consent Form(s), describing in detail the trial procedures and any risks will be approved by a Research Ethics Committee (REC) and the participant will be asked to read and review the document. Upon reviewing the document, the investigator will explain the research study to the participant and answer any questions that may arise. A contact point where further information about the trial may be obtained will be provided.

After being given adequate time to consider the information, the participant will be asked to sign the informed consent document. A copy of the informed consent document will be given to the participant for their records and a copy placed in the patient medical records, with the original retained in the Investigator Site File.

The patient participant may withdraw from the trial at any time by revoking the informed consent. The rights and welfare of the patient participants will be protected by

emphasising to them that the quality of medical care will not be adversely affected if they decline to participate in this study.

13.4 Study Discontinuation

The trial may be closed prematurely by the Trial Steering Committee. If termination occurs the Research Ethics Committee will be informed. Reasons for termination may include:

- The incidence or severity of SAEs/morbidity in this trial indicates a potential health hazard caused by the study treatment.
- It appears that participant enrolment is unsatisfactory with respect to quality and/or quantity or if data recording is severely inaccurate and/or incomplete.
- External evidence demanding trial termination.

14 DATA MANAGEMENT AND TRIAL MONITORING

For the HipHOP trial the responsibilities for Data Management and Monitoring of Workstream 1 data are delegated to the LCTC. Separate Data Management and Trial Monitoring Plans provide detail regarding the internal processes that will be conducted at the LCTC throughout the trial.

Data Management of Workstream 2 data is delegated to University of Manchester. See section 15.7 for further details.

14.1 Risk Assessment

In accordance with the LCTC Standard Operating Procedure, a risk assessment will be completed in partnership with the following:

- Trial Sponsor
- Chief Investigator
- Co-Investigator (WS2 lead)
- Health Economist
- LCTC personnel

In conducting the risk assessment, the contributors will consider potential patient participant, organisational and trial hazards, the likelihood of their occurrence and resulting impact should they occur.

The outcome of the risk assessment will be assigned according to the following categories:

- Type A: no higher than that of standard medical care
- Type B: somewhat higher than that of standard medical care
- Type C: markedly higher than that of standard medical care

This trial is a Non-CTIMP and the risk categories described above for CTIMPs (i.e. type A, B or C) have been applied to the HipHOP trial.

As this is a surgical intervention trial comparing CE marked hip prostheses, with no changes to the total hip arthroplasty procedure itself, it is likely it will be classed as a Type A and thus the trial will be of low risk.

14.2 Source Documents

In order to resolve possible discrepancies between information appearing in the CRF and any other patient related documents, it is important to know what constitutes the source document and therefore the source data for all information in the CRF.
The CRF will be considered the source document for data where no prior record exists and which is recorded directly in the CRF. A HipHOP source document checklist will be produced for each centre.

Date(s) of informed consent processes (including date of provision of patient information, randomisation number and the fact that the patient is participating in a clinical trial should be added to the patient's medical record chronologically.

14.3 Data Capture Methods

14.3.1 Case Report Forms

Participant CRF pages will be provided to sites for local completion by members of the research team trained and delegated the duty. Study staff named at each site will enter data from source documents corresponding to a participant's visit onto the relevant CRF in the participant's folder. All data requested on the CRF **must** be recorded and all missing data must be explained. Unexplained missing data will be queried. A copy of all CRFs should be retained at site. Any corrections should be made in accordance with GCP.
In relation to the PROM data, the PROM questionnaires are a source document and **sites should photocopy them** in order to retain a copy at site before posting originals to LCTC.

14.4 Monitoring

Monitoring is conducted to ensure protection of patients participating in the trial and all aspects of the trial (procedures, trial intervention, and data collection) are of high quality and conducted in accordance with sponsor and regulatory requirements.

A detailed Trial Monitoring Plan will be developed and agreed by the TMG and CI to describe who will conduct the monitoring, at what frequency monitoring will be done, and what level of detail the monitoring will be conducted to. This will be dependent on the documented risk assessment of the trial which determines the level and type of monitoring required for specific hazards. All processes may be subject to monitoring, e.g. enrolment, consent, adherence to trial interventions, accuracy and timeliness of data collection etc.

14.4.1 Central Monitoring at LCTC

There are a number of central monitoring activities that will be undertaken by LCTC and these activities are described in detail in the Trial Monitoring Plan, Data Management Plan and Data Entry and Cleaning Manual. These monitoring activities will ensure the reliability and validity of trial data.

Site monitoring visits may be 'triggered' in response to concerns regarding study conduct, participant recruitment, outlier data or other factors as appropriate.

14.4.2 Clinical Site Monitoring

In order to perform their role effectively, should monitors and persons involved in Quality Assurance and Inspection be required to conduct on-site clinical monitoring they will need direct access to primary subject data, e.g. patient records, laboratory reports, appointment books, etc. Because this affects the patient participant's

confidentiality, this fact is included on the Patient Information Sheet and Informed Consent Form.

14.4.3 Confidentiality

This trial will collect personal data (e.g. participant names), including special category personal data (i.e. participant medical information) and this will be handled in accordance with all applicable data protection legislation. Data (including special category) will only be collected, used and stored if necessary for the trial (e.g. evidencing provision of consent, for data management and central monitoring, statistical analysis, regulatory reporting, etc.). At all times, this data will be handled confidentially and securely.

CRFs will be labelled with a unique trial number. Verification that appropriate informed consent is obtained will be enabled by the provision of copies of participant's signed informed consent forms being supplied to the LCTC by recruiting sites. This transfer of identifiable data is disclosed in the PIS and ICF.
N.B. Consent forms must be transferred separately to any other trial documentation to ensure the pseudonymisation of special category data is maintained.

Site-specific study-related information will be stored securely and confidentially at sites and all local relevant data protection policies will be adhered to.

The University of Liverpool is registered as a Data Controller with the Information Commissioners Office. The LCTC as part of The University of Liverpool will preserve the confidentiality of participants taking part in the study.

The University of Liverpool, The University of Manchester and Wrightington, Wigan and Leigh Teaching Hospitals NHS Foundation Trust (Sponsor) are all acting as joint Data Controllers for HipHOP.

Breaches of data protection principles or regulations identified by any of the joint Data Controller's will be promptly notified to all other joint Data Controller's. The organisation(s) that is/are responsible for any breach will also report it to their Data Protection Officer and appropriate processes followed.

14.4.4 Quality Assurance and Quality Control of Data

To assure protocol compliance, ethical standards, regulatory compliance and data quality, as a minimum, the following will occur:

- The PI and other key staff from each centre will attend initiation training, which will incorporate elements of trial-specific training necessary to fulfil the requirements of the protocol.
- The TMG will determine the minimum key staff required to be recorded on the delegation log in order for the centre to be eligible to be initiated.
- The trial coordinator at the LCTC will verify appropriate approvals are in place prior to initiation of a centre and the relevant personnel have attended the trial specific training. A greenlight checklist will verify all approvals are in place prior to trial initiation at LCTC and the individual centre.
- The trial will be conducted in accordance with procedures identified in the protocol.

- Independent members of the TSC will provide independent oversight of the trial.
- The TMG will monitor screening, randomisation and consent rates between centres and compliance with the protocol.
- Data quality checks and monitoring procedures will be undertaken in line with the trial Data Management Plan.

14.5 Records Retention

The retention period for the HipHOP study data and information is ten years from the official End of Trial date (defined in section 8.1.2).

The PI at each investigational site must make arrangements to store the essential trial documents (as defined by ICH GCP guidelines) including the Investigator Site File and applicable participant medical records for the full length of the trial's retention period, and will arrange for confidential destruction at the end of this period as instructed by the LCTC.
The PI is also responsible for archiving all relevant source documents so that the trial data can be compared against source data after completion of the trial (e.g. in case of inspection from authorities). They must ensure the continued storage of the documents, even if they, for example, leave the hospital or retire before the end of required storage period. Delegation of responsibility for this must be documented in writing.

All other persons and organisations involved in the trial will be responsible for storing and archiving the parts of the TMF relevant to their delegated duties.

The LCTC undertakes to archive as per their contractual requirements; documents will be archived in compliance with the principles of GCP. All electronic CRFs and trial data will be archived onto an appropriate media for long term accessible storage. Hard copies of data will be boxed and transferred to secure premises where unique reference numbers are applied to enable confidentiality, tracking and retrieval.

WORKSTREAM 2

(Referred to as ‘Part 2’ in participant documentation)

15 STUDY DESIGN

15.1 Study participants

Semi-structured qualitative interviews conducted with
1) patients who were invited to take part in Workstream 1
2) health professionals who have recruited patients to Workstream 1 and/or have collected patient self-reported data
3) consultant orthopaedic surgeons.

15.2 Eligibility Criteria

Inclusion:
Patient sample:

1. Have been approached to take part in Workstream 1.

Surgeon sample:

2. Consultant orthopaedic surgeon at a Workstream 1 site or a potential site for a future full trial.

Health professional sample:

3. Involved in recruiting to Workstream 1 and/or collecting patient self-reported data.

Exclusion:
All participants:

1. Hearing impairment that precludes communication by standard telephone.

15.2.1 Patient participant interviews

Up to 30 patient participants will be recruited. All will be individuals who were approached to take part in Workstream 1 and so will meet the inclusion criteria for Workstream 1. Participants will be purposively sampled to ensure:

- Participation of patients who were randomised for the study and individuals who declined to take part in Workstream 1 but still received (or intended to receive) hip replacement
- Patients receiving surgery at both of the feasibility study sites
- Variation in the sample by age and gender.

Participants will be recruited until data saturation is reached: the point at which conducting additional interviews leads to no major new topics arising in interviews. It is expected that a sample of 20-30 individuals will be large enough to gain a range of perspectives and a rich understanding of individuals' experiences and understanding, while being small enough to effectively manage the dataset given the level of detail and depth in such data.

It is possible that people who decline to take part in Workstream 1 might also be unwilling to take part in Workstream 2 (i.e. people who do not wish to take part in research may not want to take part in either stream). We will therefore keep a record of reasons given for declining to take part in either Workstream and incorporate these

reports into the data synthesis (the recruiting health professionals will ask people why they have chosen not to take part).

15.2.2 Health professional participant interviews

Health professionals who are involved in recruiting participants to Workstream 1 and/or collecting patient self-report data will be interviewed. We anticipate that approximately nine health professionals will be employed on the study across the sites. All will be invited to take part in an interview.

Interviews with health professionals will be conducted as late as possible in the qualitative data collection period to ensure that they have maximal experience of recruiting patient participants and/or collecting data for Workstream 1.

Should any concern or allegation regarding possible malpractice occur during an interview, the details shall be provided to the Chief Investigator who will decide how to proceed and what, if any, further action should be taken.

15.2.3 Surgeon participant interviews

Approximately 20-30 consultant orthopaedic surgeon participants will be interviewed. They will be purposively sampled to include surgeons from the WS1 study sites who do and do not consent to their patients being randomised, and surgeons from hospitals that are not participating in Workstream 1 but which would be potential study sites in a definitive RCT.

It is anticipated that this sample size will be sufficient to gain a range of perspectives relevant to acceptability of a trial to surgeons while also ensuring a manageable data-set to achieve an in-depth and meaningful analysis.

To maximise their experience, interviews with surgeons who have recruited patient participants to Workstream 1 will be conducted as late as possible in the qualitative data collection period. Surgeons who are not participating in the recruitment of patient participants can be interviewed at any stage of the data collection process.

Should any concern or allegation regarding possible malpractice occur during an interview, the details shall be provided to the Chief Investigator who will decide how to proceed and what, if any, further action should be taken.

15.3 Enrolment

15.3.1 Patient participants

Patients first approached to take part in WS1 via clinic visit

Where the first contact with the patient is an in-person discussion with a health professional at the clinic, the health professional will first introduce the patient to WS1. On completion of the discussion about WS1 (which may or may not finish with informed consent), with the aid of a leaflet, the health professional will introduce the patient to WS2 – the qualitative interview study. **They will introduce all patients to WS2, both patients who accepted the invitation to take part in WS1, and also those who declined.** There will be a brief paragraph in the WS1 PIS introducing the qualitative interview study, and health professionals and patients will also be provided with a short leaflet outlining key information regarding the qualitative interview study.

Patients will be asked if they might be interested in taking part in a phone interview. If they express interest, they will be asked if they would be happy for the healthcare professional to pass their details on to the research team so that the research team can contact them with more information. They will be advised that we are looking to interview 20-30 people with a mixture of characteristics, so it is possible that they might not be asked to take part in an interview.

If they agree for the health professional to pass their details on to the research team, the health professional will complete a form with the patient to obtain the following details:

- Name
- HipHOP trial number
- Proposed date of surgery
- Email or postal address (patient's preferred way to be sent the study information)
- Phone number
- Whether they have expressed interest and/or consented to take part in WS1
- Gender
- Age
- Hospital
- Confirmation that they are happy for information about their surgery date to be shared with the University of Manchester research team.

The patient will be asked to sign the form to confirm they are providing consent for these details to be shared with the University of Manchester research team. The details collected will be shared by email with the University of Manchester research team at interviews.hiphop@manchester.ac.uk. Details must be transferred by secure email, i.e. '[SECURE]' must be the first word of the subject line, written in capital letters, and surrounded by [square] brackets. Alternatively, details can be provided in a password protected spreadsheet that is sent by insecure email, however utilising both methods is preferred where possible. **Note:** The provision of passwords to unlock the security measures must be provided via a different means of communication, e.g. telephone call. Forms will be destroyed on completion of WS2 data collection.

Patients first approached to take part in WS1 by posting of PIS followed up by phone call:

For patients who are identified from waiting lists for WS1, and for whom the first contact from the research team is via a posted PIS and telephone call, the short leaflet about WS2 will be included with the WS1 PIS. On the phone, the health professional will first discuss WS1 with the patient and establish their interest for taking part in WS1. The health professional will then refer the patient to the WS2 leaflet, give an outline of the qualitative interview study, and ask if they might be interested in taking part in a phone interview.

If the patient expresses interest, one of two methods will then be followed. Method 1 will initially be followed, but if this proves to be unfeasible in practice, Method 2 will be followed.

Method 1: consenting for detail sharing when admitted for surgery

During the phone call, health professionals will make a note of the person's interest and inform them that they will meet with them when they are admitted for surgery to ask them to consent to the healthcare professional sharing details about them with the University of Manchester research team. The healthcare professional will then meet with the person at the hospital (after admission for surgery but before surgery), review the WS2 leaflet with them, and ask if they are still interested in taking part in an interview such that they would like to receive further information. They will be asked if they would be happy for the healthcare professional to pass their details on to the research team so that the research team can contact them with more information. They will be advised that we are looking to interview 20-30 people with a mixture of characteristics, so it is possible that they might not be asked to take part in an interview. The healthcare professional will then complete the details collection form with the patient and sharing it with the University of Manchester research team, as outlined above (for patients first approached in a clinic)

Method 2: consenting for detail sharing by post.

The patient will be alerted to the details collection form included in their information pack. The healthcare professional will talk through the form with the patient and advise them to place it in the enclosed pre-paid envelope and post it back to the University of Manchester research team.

All approaches:

Patients who have expressed interest in, or consented to, taking part in Workstream 1.

Following receipt of patient details, the research team will contact the LCTC to gain information about the patient's surgery date.

Approximately 1 week post-surgery, the WS2 PIS will be posted to the patient, and followed up with a phone call from the research team (timed to ensure that at least 24 hours will have passed between receipt of the information sheet and the phone call). During this phone call, the researcher will explain what WS2 is about, go through the content of the PIS, answer any questions the participant might have, and arrange a date and time for the phone interview. The interviews will be conducted after surgery to ensure that the participant has experienced completing baseline questionnaires prior to being interviewed.

See also section 15.3.4.

Patients who have declined participation in Workstream 1

The research team will send the Workstream 2 PIS to the patient. If the surgery date is known and there is not time to send the PIS before surgery, it will be posted approximately 1 week after surgery. This will be followed up with a phone call from the research team (timed to ensure that at least 24 hours will have passed between receipt of the information sheet and the phone call). During this phone call, the researcher will explain what WS2 is about, go through the content of the PIS, answer any questions the participant might have, and arrange a date and time for the phone interview. There is no requirement for these participants to have undergone surgery before taking part

in an interview, so the interview can be arranged at any time convenient to the participant, before or after surgery.

See also section 15.3.4.

15.3.2 Healthcare professional participants

Healthcare professionals will be emailed by a University of Manchester researcher with an invitation to take part and a copy of the participant information sheet. This email will be followed up by email or a phone call (at least 24 hours after the healthcare professional will have received the information sheet) to see if they have any questions and to learn whether they would like to take part in an interview. The researcher will send up to two reminders should no response be received.

See also section 15.3.4.

15.3.3 Surgeon participants

At the sites participating in Workstream 1, potential surgeon participants will be identified by the site principal investigator (both surgeons who are, and who are not, allowing their patients to be randomised for the feasibility study). The HipHOP Chief Investigator, Professor Tim Board, will email those surgeons with a study participant information sheet, introducing the University of Manchester researcher.

At other sites (not participating in Workstream 1 but likely additional sites for a definitive trial), the HipHOP Chief Investigator, Professor Tim Board, will email contacts at those sites to ask for details of suitable surgeons. He will then email those surgeons with a study participant information sheet and introduce the University of Manchester researcher.

For all surgeons, after at least 24 hours to consider the study information, the University of Manchester researcher will contact each surgeon to ask if they have any questions about the study and to invite them to take part in an interview. A date/time for phone interviews will be arranged where individuals express interest.

The researcher will send up to two reminders should no response be received and insufficient participants have been recruited.

See also section 15.3.4.

15.3.4 All participant Groups

If an individual informs the researcher that they do not wish to take part in an interview, the interviewer will ask what the reason for this is, and note the reason. All individuals will be reminded that they do not need to give a reason.

Before the start of the interview, the researcher will go over the content of the information sheet with the participant, and take consent over the phone. The researcher will read out each consent item, and the participant will be asked to indicate if they agree with each point – these responses will be audio-recorded. After completing the consent process, the audio-recorder will be stopped. On starting the interview, a new audio-recording will be recorded. This will enable the consent recording (containing identifiable details and requiring long-term storage) to be stored

separately from the interview audio-recording (which will be kept until data analysis is completed and then destroyed, leaving only a pseudonymised transcription).

15.4 Data collection procedures

15.4.1 Patient participant interviews

Interviews will be conducted no less than two weeks after surgery, and usually within four weeks of surgery for individuals who take part in Workstream 1, and at a mutually convenient time for individuals who decline to take part in Workstream 1. Interviews will be carried out by telephone and will usually last between thirty minutes and one hour, depending on how much the participant would like to say. The interviewer will use an interview schedule to guide interviews; this will focus on patients' experiences of being approached for the study, understandings of the research and reasons for deciding whether or not to participate. Participants who consented to taking part in Workstream 1 will also be asked about experiences of being randomised and participating in Workstream 1. Questions will be open-ended such that the interview will focus on issues in line with the research objectives, but participants will be able to talk freely and raise issues that may not have occurred to the research team. Interviews will be audio-recorded and transcribed verbatim by a University of Manchester approved transcription company. All professionally transcribed interviews will be carefully checked against the audio-recording for accuracy by a member of the research team. During this process, transcriptions will be pseudonymised (identifiable details e.g. person names, place names will be removed).

15.4.2 Healthcare professional interviews

Healthcare professionals will be interviewed by telephone; interviews will last for approximately 30 minutes. An interview schedule will be used to guide interviews. The interview will address: experiences of recruiting patient participants to the HipHOP trial, thoughts about patient perceptions of the HipHOP study (including perceptions of reasons for agreeing or declining to take part), experiences of data collection and healthcare professionals' thoughts about the HipHOP study. Interviews will be audio-recorded and transcribed verbatim by a University of Manchester approved transcription company. All professionally transcribed interviews will be carefully checked against the audio-recording for accuracy by a member of the research team. During this process, transcriptions will be pseudonymised (identifiable details e.g. person names, place names will be removed).

15.4.3 Surgeon participant interviews

Surgeon participants will also be interviewed by telephone. Interviews will last for approximately 30 minutes. An interview schedule will be used to guide interviews which will focus on surgeon participants' beliefs about the treatment options, perceptions and experiences of research in general, their thoughts about this particular project, their opinions about the appropriateness of randomizing participants in this context, and thoughts about barriers (and facilitators) to implementing any guidance that results from a full trial. Surgeon participants at the study site will be asked about their reasons for opting in or opting out of allowing their patients to be included in the research. Interviews will be audio-recorded and transcribed verbatim by a University of Manchester approved transcription company. All professionally transcribed interviews will be carefully checked against the audio-recording for accuracy by a member of the research team. During this process, transcriptions will be pseudonymised (identifiable details e.g. person names, place names will be removed).

15.5 Analysis

Analysis of Workstream 2 data will be conducted by the University of Manchester research team. Thematic analysis will be conducted to identify and understand 'patterns' in the data[25]. We will prioritise the voice of participants, and focus on the issues that appear to be important to them. An inductive, data-driven approach will be taken, aiming to understand the experiences and perceptions of participants in relation to the research (patients, healthcare professionals and surgeons) and implementation of findings (surgeons). 'Framework' will be used to structure the analysis process[26]. This is a systematic and transparent approach which can be particularly beneficial in enabling other researchers within multidisciplinary teams to follow the process and decisions taken by the analyst. The Framework approach includes 'charting', the summarizing of data in tables. The researcher uses these tables in making sense of the various perceptions voiced by participants within themes, and in understanding how themes relate to each other.

An aspect of the qualitative work will be to identify and understand potential barriers to implementation in practice. On completion of the inductive analysis, when and if appropriate, we will relate our findings to theoretical frameworks for implementation in health care contexts, and may use such structures to develop an implementation framework specific to our research context.

15.6 Ethical Considerations

15.6.1 Confidentiality and Anonymity

These issues are particularly pertinent in this project because in order for people to speak openly about their experiences and thoughts regarding the trial, participants need to feel confident that they will not be at risk of judgement or negative consequence by their care team (patient participants) or colleagues (surgeon participants).

For patient participants, the initial approach and consenting will usually be conducted by healthcare professionals at NHS sites, so it will not always be possible to ensure that no one in the care team knows who has taken part. For surgeon participant interviews, the initial contact will be made by the HipHOP Chief Investigator, a consultant orthopaedic surgeon, who may therefore be able to guess who is taking part in interviews.

However, to ensure that members of care teams/clinical colleagues cannot identify who says what in interviews, the arranging of interviews, the conduct of interviews and management, analysis, and storage of data will be managed by the University of Manchester research team. Interviews will be recorded on encrypted audio-recorders and uploaded onto the secure University of Manchester server. Secure methods will be used to share data with a professional transcription service (who will meet University of Manchester standards for data management). As soon as possible, the transcription will be checked and pseudonymised by a University of Manchester researcher: any identifying details (e.g. names, locations) will be removed from the transcript and the participant will henceforward only identified by a participant number. Members of the research team who are also care team members will not have access to full interview transcripts as it is possible that, even after removal of identifying details, there could be contextual information about experiences from which someone who has worked with the participant could identify the individual.

Data extracts may be shared with clinical and other members of the research team during the analysis process to gain their thoughts on the data and the interpretation of that data, but any extracts will be carefully selected to ensure that the individual cannot be identified.

In the participant information sheets, it will be made clear who has access to what information about participants at each stage.

It may be appropriate to break confidentiality if, when conducting interviews, the researcher becomes concerned that any individual might be at risk of harm. For patient participants, the research team would inform the patient's care team of any such concerns. For surgeon and healthcare professional participant interviews, should clinical practice be mentioned that would raise concern, the HipHOP Chief Investigator will be informed. A clear explanation of circumstances which could lead to confidentiality being broken will be provided on participant information sheets.

Study consent audio recordings will be stored by the University of Manchester team, in a password-protected folder on the secure University of Manchester server. Audio consent forms will be stored separately from data, and any details that may link consent forms with data will be removed from the data set.

The research team will also need to store participants' names and contact details in order to arrange and conduct interviews. These will be securely stored until completion of the research project and then destroyed.

15.6.2 Distress

While the topics being discussed in the patient participant interviews are not anticipated to cause distress, it is possible that, when discussing their experiences of surgery, the trial, and recovery, patient participants could talk about issues they find upsetting such as worries about surgery or pain. Should any participant show signs of distress then the study distress policy will be followed.

15.6.3 Fatigue

It is possible that some patient participants will be experiencing post-operative fatigue at the time of the interview. It will be made clear to patients (in the participant information sheet and by the researcher at the start of the interview) that they can take as many breaks as they need to, and/or split the interview over multiple days. The researcher will check with the participant part way through the interview if they're still feeling well and wishing to continue or if they wish to take a break.

15.6.4 Withdrawal

All participants will be informed that they are free to withdraw from the interview, without giving a reason and without detriment to them, at any time before or during the interview. They will also be free to withdraw from the interview after the study up to two weeks after their participation (after this time their data will be integrated into the analysis process).

Should a patient lose capacity after being interviewed the information they provided during the interview will still be used for analysis. This is regardless of whether they withdraw from Workstream 1.

15.6.5 Ethical Approval

Workstream 2 will be submitted for ethical approval through the NHS research ethics and HRA approval process, within the same documentation as Workstream 1.

15.6.6 Informed Consent Process

This is detailed under 'enrolment' above, see section 15.3.

15.7 Data Management

15.7.1 Direct access to data

The University of Manchester is responsible for data collection, management and storage for all Workstream 2 data. The University of Manchester research team will produce pseudonymised data transcripts; these transcripts will be securely stored on the University of Manchester server and only accessed by University of Manchester members of the research team. With participant consent, access by future University of Manchester researchers, where the aims of researchers and data management procedures are consistent with the current project, will also be permitted.

Where official access to data is required for standard research data monitoring, Quality Assurance or Inspection purposes, e.g. to recordings, transcriptions etc., this will also be permitted. Participants are advised of this via the Participant Information Sheets.

15.7.2 Confidentiality

This is detailed with the Ethical Considerations, see section 15.6.

15.7.3 Quality assurance and quality control of data

Data will be managed and quality controlled in accordance with standard University of Manchester data management procedures.

Wrightington, Wigan and Leigh Teaching Hospitals NHS Foundation Trust, the University of Liverpool and the University of Manchester and will enter into a tri-party data sharing agreement as joint Data Controllers. Specifics of data sharing requirements will be detailed and agreed within this contract.

15.7.4 Records retention

Interview audio-recordings and details collection form information will be held securely on the University of Manchester server until data analysis is complete, and will then be destroyed. After completion of the research, consent audio-recordings and all interview transcripts will be stored for ten years and then destroyed.

15.8 Contingency planning

In the event of a national emergency (e.g. COVID-19) which prevents the University of Manchester researcher accessing their research office, the following amendments to practice will be followed:

- The UoM researcher will not print out and send PISs to interested individuals. Instead, healthcare professionals will be provided with WS2 PISs in electronic format and asked to print them.
- Where the healthcare professional introduces the individual to Workstream 2 face-to-face, after ascertaining their interest in Workstream 2 and the details collection form being completed, the healthcare professional will give the patient the WS2 information sheet for the patient to read in their own time. The individual's details will be shared with the UoM researcher as per usual procedures. When the researcher phones the individual, they will talk through the information sheet with the patient, answer questions, and ascertain interest in the study as per usual procedures.
- For patients who are approached by post and phone (by the healthcare professional),
    - Method 1: the WS2 PIS will be included with other study materials. During the phone call, after ascertaining interest in WS2, the healthcare professional will encourage the individual will be to read the PIS in their own time. The details collection form will be shared with the UoM researcher, who will contact the participant by phone as detailed above.
    - Method 2: the WS2 PIS will be included with study materials as per Method 1, and patients will be asked to complete the details collection form at home. Instead of returning this by post to the UoM research team, they will be asked to return it by post to the hospital research team, who will then share the details with UoM researchers using the established procedures.
- In standard procedures, it is possible that some phone interviews could be conducted from the researcher's own home, and some analysis could be conducted from researchers' homes (in line with UoM data protection policies). If the researcher cannot access UoM offices, all data collection and analysis will be conducted from researchers' homes.

16 INDEMNITY

HipHOP is sponsored by Wrightington, Wigan and Leigh Teaching Hospitals NHS Foundation Trust and coordinated by the LCTC in the University of Liverpool.

As this is an investigator-initiated, non-CTIMP study, The Association of the British Pharmaceutical Industry (ABPI) guidelines for patient participant compensation by the pharmaceutical industry do not apply.

Wrightington, Wigan and Leigh Teaching Hospitals NHS Foundation Trust is independent of any pharmaceutical company, and as such, it is not covered by the ABPI guidelines for patient compensation. Furthermore, Wrightington, Wigan and Leigh Teaching Hospitals NHS Foundation Trust does not hold insurance against claims for compensation for injury caused by participation in a clinical trial and they cannot offer any indemnity. However, in terms of liability, NHS Trust and Non-Trust Hospitals have a duty of care to patients treated, whether or not the patient is taking part in a clinical trial, and they are legally liable for the negligent acts and omission of their employees. Compensation is therefore available in the event of clinical negligence being proven.

Clinical negligence is defined as “A breach of duty of care by members of the health care professions employed by NHS bodies or by others consequent on decisions or judgments made by members of those professions acting in their professional capacity in the course of their employment, and which are admitted as negligent by the employer or are determined as such through the legal process”.

Wrightington Wigan and Leigh Teaching Hospitals NHS Foundation Trust has in place Clinical Trials indemnity coverage for this trial which provides cover to the NHS Foundation Trust for harm which comes about through the Trusts, or its staffs, negligence in relation to the design or management of the trial and may alternatively, and at the trust’s discretion provide cover for non-negligent harm to patient participants.

With respect to the conduct of the trial at Site and other clinical care of the patient, responsibility for the care of the patient participants remains with the NHS organisation responsible for the Clinical Site and is therefore indemnified through the NHS Litigation Authority.

HipHOP has three joint Data Controllers, as stipulated below. All Data Controllers have contractual agreements with the Sponsor regarding responsibilities in the sharing and protection of patient data.

- University of Liverpool
- University of Manchester
- Wrightington, Wigan and Leigh Teaching Hospitals NHS Foundation Trust

17 FINANCIAL ARRANGEMENTS

HipHOP is a non-commercial, investigator-initiated and investigator-led trial. No direct payments are available to cover costs associated with participant recruitment, treatment administration, follow-up visits or patient participant travel expenses. Nominal payments will be provided to patient participant recruiting sites only to cover the cost of CRF printing and postage. These payments are detailed within the research site agreement between the sponsor and recruiting site.

The trial is funded by the National Institute for Health Research, Research for Patient Benefit programme; consequently having automatic endorsement from the NIHR Clinical Research Network (NIHR CRN; CRN). The CRN will be responsible for providing local investigators with the necessary research infrastructure.

18 TRIAL OVERSIGHT COMMITTEES

18.1 Trial Management Group (TMG)

The composition of the TMG is as listed below. Membership details are available from the Trial Coordinator via email to hiphop@liverpool.ac.uk.

Chief Investigator
Qualitative Co-applicant
Health Economics Co-applicant
Patient Outcomes Co-applicant
Trial Statistician
Principal Investigator (WS1)
Trial Coordinator
Sponsor Representative
Sponsor Research Nurse
LCTC Senior Management Representative

The role of the TMG is to monitor all day-to-day aspects of the conduct and progress of the trial, ensuring the trial protocol is adhered to and to take appropriate action to safeguard participants and the quality of the trial itself.

The TMG will meet a minimum of 4 times a year and will provide recommendations to the TSC concerning any aspect of the trial.

18.2 Trial Steering Committee (TSC)

The composition of the TSC, which meets the funder's specification of 75% independence, is as listed below. Membership details are available from the Trial Coordinator via email to hiphop@liverpool.ac.uk.

Independent Chairperson Expert in the field of Orthopaedic Surgery
Independent Expert in the field of Orthopaedic Surgery
Independent Health Economist
Independent Qualitative Researcher
Independent Statistician
Independent Patient and Public Involvement Representative
Chief Investigator
Trial Statistician

Although not members of the TSC, the Lead of the Qualitative Workstream, the Trial Coordinator, and Sponsor Representatives will also attend and actively participate in meetings as guests of the Chair, but will not be allowed to vote.

The role of the TSC is to provide overall supervision of the trial on behalf of the Sponsor and Funder and to ensure that the trial is conducted to the rigorous standards set out in the Department of Health's Policy Framework for Health and Social Care Research.

The TSC is obliged to meet at least annually.

18.3 Independent Safety and Data Monitoring Committee (ISDMC)

The need for an ISDMC has been considered by sponsor and has been determined as unnecessary as this is a trial that presents no greater risk than usual care and is using CE marked devices for their intended purpose in a well-established surgical procedure. In addition, the short duration of both recruitment and follow-up means that all participants will be recruited and received intervention before meaningful results would be available. .

The Independent TSC will take on the responsibility for reviewing and assessing participant recruitment, provide independent oversight of the monitoring of safety/intra- and post- operative complications, trial conduct and external data and will make recommendations regarding trial conduct and continuity to the TMG and Sponsor.

19 PUBLICATION AND DISSEMINATION

Authors of any publication must acknowledge that the trial was performed with the support of:

NIHR Research for Patient Benefit programme
Wrightington, Wigan and Leigh Teaching Hospitals NHS Foundation Trust
The RCSEng North West Surgical Trials Centre
The University Bristol
The University of Liverpool
The University of Manchester
The University of Oxford
All hospital trusts (by name) that recruited patients, surgeons or healthcare professionals

The results from different recruitment sites will be analysed together and published as soon as possible. Individual researchers must undertake not to submit any part of their individual data for publication without the prior consent of the Trial Management Group.

The Trial Management Group will form the basis of the Writing Committee and advise on the nature of publications. The Uniform Requirements for Manuscripts Submitted to Biomedical Journals (http://www.icmje.org/) will be respected.

All publications shall include a list of those whose role was pertinent to the management of the trial workstream the publication refers to, and if there are named authors, these should be decided by mutual consent. The ISRCTN allocated to this trial must always be attached to any publications resulting from it.

The members of the TMG and TSC should be listed with their affiliations in the Acknowledgments/Appendix of the main publication.

Any secondary publications and presentations prepared by the investigators must be reviewed and authorisation given in writing by the HipHOP Trial Management Group (TMG). Final manuscripts must be submitted to the HipHOP TMG in a timely fashion and in advance of being submitted for publication, to allow time for review and resolution of any outstanding issues.

20 CHRONOLOGY OF PROTOCOL AMENDMENTS

20.1 Version 1 (22 June 2020)

Original Approved version.

20.2 Version 2 (04 November 2020)

a. Addition of Clinical Coordinator;
b. Site/Clinician inclusion criteria updated to indicate the Research Site Agreement is now a stand-alone document;
c. AESI event corrected to '….acetabular *or* pelvic fracture (postoperative)';
d. AESI event 'venous thrombosis' changed to 'pulmonary embolism';
e. Email address for reporting SADEs updated, with added guidance on how to encrypt the email;
f. Email address for sending identifiable contact details for patients to UoM updated, with added guidance on protecting the data;
g. Correction to the full title of an ISDMC, expansion to the justification for an ISDMC not being necessary ;
h. Clarification that the TSC will provide independent oversight of safety reporting;
i. Increase to the number of sites participating in WS1;
j. Update to stats/interview language as a result of point 'i';
k. Requirement to re-consent WS1 patient participants if THA does not occur within 56 days replaced with a verbal reaffirmation of consent.

20.3 Version 3 (29 April 2021)

a. Reduction of longer term WS1 post-operative follow-up period from 6 months to 3-6 months;
b. Patient participants to WS1 will be withdrawn if their surgery is delayed beyond the cut-off point required to collect follow-up data at 3 months post-surgery;
c. The pool of interviewees for the WS2 qualitative interviews with research nurses is expanded to include all healthcare professionals involved in the WS1 recruitment process;
d. Flexibility added so interviews with patient participants who participate in WS1 will occur usually within 2-4 weeks post-operation.

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22 DOCUMENTS SUPPLEMENTARY TO THE PROTOCOL

Documents referenced within the protocol are separately maintained and version controlled. Any of the documents subject to HRA and REC review are submitted as separate version controlled documents.