Trial Title: Does the Corin Optimised Positioning System improve clinical outcome in total hip arthroplasty? A multi-centre, two-arm randomised control trial

Internal Reference Number / Short title: The HAPI Study (Hip Arthroplasty Positioning Improvement)

Ethics Ref: 17/SC/0506

IRAS Ref. 216084

Date and Version No: 10/11/2017 v1.2

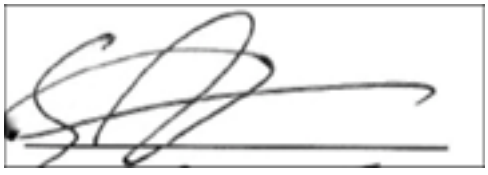
Chief Investigator: Professor Siôn Glyn-Jones
Professor of Orthopaedic Surgery and Consultant Orthopaedic Surgeon, University of Oxford

Co-investigators Mr Adrian Taylor, Consultant Orthopaedic Surgeon, Oxford University Hospitals NHS Foundation Trust
Mr Ben Kendrick, Consultant Orthopaedic Surgeon, Oxford University Hospitals NHS Foundation Trust
Dr Rory Ferguson, Clinical Research Fellow, University of Oxford
Complete list of study team members and participating site contact details on file

Sponsor: University of Oxford
Clinical Trials & Research Governance
Joint Research Office,
Block 60,
Churchill Hospital
Old Road,
Headington
Oxford, OX3 7LE

Funder: Corin Limited

Chief Investigator Signature:



Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, HRA, host organisation (Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford), and members of the Research Ethics Committee, unless authorised to do so. There are no conflicts of interest to declare.

TABLE OF CONTENTS

1. KEY TRIAL CONTACTS

Chief Investigator	Professor Siôn Glyn-Jones Nuffield department of Orthopaedics, Rheumatology and Musculoskeletal science, NIHR Bio-Medical Research Unit, Oxford University OX3 7LD Sion.glyn-jones@ndorms.ox.ac.uk 01865 737839
Sponsor	University of Oxford Clinical Trials & Research Governance Joint Research Office, Block 60, Churchill Hospital Old Road, Headington Oxford, OX3 7LE
Clinical Trials Unit	Nuffield department of Orthopaedics, Rheumatology and Musculoskeletal science, NIHR Bio-Medical Research Unit, Oxford University

	OX3 7LD 01865 227374 brc.reception@ndorms.ox.ac.uk

2. SYNOPSIS

Trial Title	Does the Corin Optimised Positioning System improve clinical outcome in total hip arthroplasty? A multi-centre, two-arm randomised controlled trial	
Internal ref. no. (or short title)	The HAPI Trial	
Trial Design	Single-blinded randomised controlled trial comparing best practice total hip arthroplasty (THA) surgical technique and templating with the best practice THA surgical technique plus Corin Optimised Positioning System (OPS) to guide templating. We will perform an internal pilot after 100 participants have been recruited. If analysis shows the trial is feasible, we will then progress onto the full study.	
Trial Participants	Male and female adults between 18 and 85 years of age, with a dysfunctional hip caused by osteoarthritis (OA), post traumatic OA, inflammatory arthropathy, avascular necrosis and congenital/ developmental problems, randomly selected from the THA waiting list at each participating centre.	
Planned Sample Size	460 participants. 230 patients will receive best practice THA with conventional templating; the other 230 will receive best practice THA with Corin OPS to guide templating. Patients who drop out will not be replaced. The first 100 patients will constitute an internal pilot: results of the internal pilot will be used to repower the study. We anticipate the projected sample size of 460 may change by 5% either way.	
Treatment duration	2 years	
Follow up duration	1 year	
Planned Trial Period	3 years	
	Objectives	Outcome Measures
Primary	*To compare the efficacy of the Corin OPS system to guide templating in THA with standard templating in THA in reducing dislocation*	Dislocation rate and re-operation for dislocation rate
Secondary	1, To determine whether the Corin OPS System improves Harris hip score, patient reported outcome measures (PROMs), reduces hospital stay and normalises gait more effectively than conventional surgery	1, PROMs: • Oxford hip score (OHS) • iHOT33 • HAGOS • Pain detect • EQ5D • UCLA score

	2, To determine whether the Corin OPS System improves leg length discrepancy compared to conventional surgery 3, To quantify the cost of Corin OPS within the clinical pathway and perform a full health economic analysis following surgery 4, To determine the reproducibility of the Corin OPS templating technique at implanting the acetabular cup into the planned position. This will be performed in a subgroup of 50 patients randomly selected from the OPS arm to undergo a post-operative CT scan 5, To determine whether the Corin OPS System increases operation duration compared to conventional surgery	Harris hip score (HHS) Length of hospital stay Gait analysis Cost analysis 2, Leg length measurement 3, Cost 4, Post-operative position of prosthesis measured relative to planned position, based on pre- and post-operative CT scans 5, Operation duration

3. ABBREVIATIONS

AE	Adverse event
AR	Adverse reaction
CI	Chief Investigator
CRF	Case Report Form
CT	Computed Tomography
CTRG	Clinical Trials and Research Governance
DMC	Data Monitoring Committee
EQ-5D	Euro-Qol Group 5-Dimensions Questionnaire
GCP	Good Clinical Practice
GP	General Practitioner
HAGOS	Copenhagen Hip and Groin Outcome Score
HHS	Harris Hip Outcome
HRA	Health Research Authority
ICF	Informed Consent Form

ICH	International Conference on Harmonisation
iHOT33	International Hip Outcome Tool-33
NHS	National Health Service
NRES	National Research Ethics Service
OA	Osteoarthritis
OHS	Oxford Hip Score
OPS	Optimised Positioning System
PI	Principal Investigator
PIL	Participant/ Patient Information Leaflet
PROM	Patient Reported Outcome Measure
R&D	NHS Trust R&D Department
REC	Research Ethics Committee
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
THA	Total Hip Arthroplasty
TMF	Trial Master File
UCLA score	University of California, Los Angeles Activity Score

4. BACKGROUND AND RATIONALE

Osteoarthritis (OA) is the most common joint disease worldwide affecting an estimated 10% of males and 18% of females over 60 years of age[1]. The resultant pain and loss of function can be debilitating and in developed countries represents a large socioeconomic burden, costing between 1% and 2.5% of gross domestic product, which currently stands at over £1.5 trillion[2]. Total hip arthroplasty (THA) is an effective treatment for end-stage hip arthritis; however, demand for the procedure is growing rapidly, fuelled by an ageing population and the obesity epidemic[3]. In fact, rates of THA are predicted to rise 174% between 2005 and 2030[4]. The current commissioning environment in developed countries means that investment in iterative improvements of existing THA implant designs are unlikely to yield either significant benefits to patients or be supported by health funders. The two principle issues that concern surgeons and patients are the longevity of implants and the ability of new technologies to minimise complications such as dislocation and infection. The James-Lind Priorities Setting Partnership, an internationally recognised patient-driven organisation, has recently identified these pre-operative and intra-operative factors as targets for improving outcome following hip and knee replacement[5,6].

One of the largest costs to healthcare providers following THR is dislocation[7]. Although the dislocation rate reported in Joint Registries is between 1 and 3%[8,9], we know that this significantly underestimates the true problem, as the majority of dislocation events are managed with closed reduction and do not result in revision surgery[10]. It is estimated that dislocation is an order of magnitude more common than reported

in Registry data. Literature estimates indicate a true dislocation prevalence of 3 to 15%[9,11,12]. The cost of dislocation is significant as the problem is often recurrent, resulting in multiple hospital admissions. The resulting average cost for each patient who suffers a THR dislocation is around £30,000[7].

The factors that influence dislocation are poorly understood. Conventional surgical wisdom dictates that placing a cup in the Lewinneck 'safe zone' reduces both instability and wear[13]. A recent study of 9784 primary THAs, however, demonstrated that 58% of patients who suffered a dislocation had implants judged to be in a safe position[14]. This has led to suggestions that the idea of one generic 'safe zone' may be misleading[14,15]; instead, there is a unique optimum position to place a cup in each patient undergoing THA, based on the unique and complex interaction of the spine and pelvis of the individual. Thus, in some patients, whilst the acetabular cup appears well positioned by conventional measures, pelvic tilt and spinal position mean that the cup is placed in a position of instability during some activities.

The Corin Optimised Positioning System (OPS) is a novel platform, designed to enable delivery of the prosthetic acetabular cup into an optimised position for every patient undergoing THA[16]. It comprises two stages: pre-operative planning and intra-operative guidance. Pre-operatively, patients undergo dynamic imaging (computed tomography scanning and X-ray films). The information gained about the relative movements of a patient's spine, pelvis and hips are used to create a personalized physiological profile. This enables calculation of the optimized acetabular cup orientation for each individual. A unique physical guide (which falls under the definition of a custom-made device in the Medical Device Directive) is then created for each patient to fit precisely into the acetabular fossa, for use intra-operatively. Intra-operatively, the Corin OPS uses laser alignment to aid the surgeon in aligning the acetabular cup in the calculated optimised orientation. One laser is affixed to an immovable pelvic screw; the other is attached to the reverse of the acetabular cup. The target orientation of the cup is achieved when the two lasers are aligned.

The aim of this trial is to assess the efficacy of the use of the Corin Optimised Positioning System in reducing post-operative hip dislocation in patients undergoing total hip arthroplasty by comparing it with current standard templating in total hip arthroplasty. All total hip implants/components used in the study will be produced by Corin for uniformity and are CE marked. There is currently no evidence that this novel approach to templating has an effect on dislocation rate. This project aims to provide evidence that this new technique can improve outcomes for patients and have the potential to reduce the need for complex, expensive revision surgery.

5. OBJECTIVES AND OUTCOME MEASURES

Objectives	**Outcome Measures**	**Timepoint(s) of evaluation of this outcome measure (if applicable)**
Primary Objective *To compare the efficacy of the Corin OPS system to guide templating in THA with standard templating in THA in reducing dislocation*	Dislocation rate and re-operation for dislocation rate	Pre-operatively, then at 3,6 and 12 months post-operatively

Secondary Objectives 1, To determine whether the Corin OPS System improves Harris hip score, patient reported outcome measures (PROMs), reduces hospital stay and normalises gait more effectively than conventional surgery 2, To determine whether the Corin OPS System improves leg length discrepancy compared to conventional surgery 3, To quantify the cost of Corin OPS within the clinical pathway and perform a full health economic analysis following surgery 4, To determine the reproducibility of the Corin OPS templating technique at implanting the acetabular cup into the planned position. This will be performed in a subgroup of 50 patients randomly selected from the OPS arm to undergo a post-operative CT scan 5, To determine whether the Corin OPS System increases operation duration compared to conventional surgery	1, PROMs: • Oxford hip score (OHS) • iHOT33 • HAGOS • Pain detect • EQ5D • UCLA Harris hip score (HHS) Length of hospital stay Gait analysis 2, Measurement of leg lengths 3, Cost of inpatient stay for THA and cost of all patient care pertaining to their THA 4, Post-operative position of prosthesis measured relative to planned position, based on pre- and post-operative CT scans 5, Operation duration	1, PROMS and HHS recorded pre-operatively, then at 3, 6 and 12 months post-operatively. Gait analysis pre-operatively and at 12 months post-operatively (25 patients in each arm). Length of hospital stay will be recorded on discharge 2, X-rays and leg lengths will be assessed pre-operatively, then at 12 months post-operatively 3, Cost calculated 12 months post-operatively 4, CT scans pre-operatively and at 12 months post-operatively 5, Recorded at end of operation

6. TRIAL DESIGN

This will be a multi-centre, two-arm, single blind (participant blind), randomised controlled group superiority study. It will take place in the NHS hospital setting. Stratification will be performed for age and sex by means of a minimisation technique during randomisation for each subject entering the trial. There will be no limit on the number of sites and no limit on the number of recruits per site. The study site shall maintain a list of the participating sites and investigators separately to the protocol.

Arm 1

Best practice total hip arthroplasty with conventional templating

Arm 2

Best practice total hip arthroplasty with Corin Optimised Positioning System to guide templating

In the study 230 participants will receive best practice THA with conventional templating; the other 230 will receive best practice THA with Corin OPS to guide templating. Any participant that withdraws from the study will not be replaced.

Initially we will perform an internal pilot study of 100 participants, with 50 participants in each arm. This will enable us to check feasibility of recruitment and to check our power calculation is correct. We anticipate recruitment to the pilot study will take six months, with an average of four participants recruited per week. Together the five centres currently recruited performed 3419 primary total hip replacements in 2015, an average of 66 per week[8]. Since participants in the two arms receive the same procedure, with the difference being in the technique used, with clear explanation of the trial to potential participants, we anticipate that approximately 50% of eligible patients that are approached will consent to take part in the trial. With this knowledge, we believe recruitment of initially four (rising to six) participants per week will be attainable. If the internal pilot study shows that completing the study is unfeasible, then the trial will be terminated following mutual agreement from both the Chief Investigator and the funder (Corin Limited). We anticipate recruitment to the full trial will take two years.

The expected duration of participant participation is 15 months. Following recruitment in outpatient clinics, participants will undergo baseline assessments, including imaging (CT scan and x-rays of pelvis) and clinical assessment. A subset of 50 participants will be randomly selected to also undergo gait analysis as part of the baseline assessments pre-operatively. All participants will then undergo THA surgery, which will likely entail an in-patient hospital stay of 1-7 days. Post-operative rehabilitation will be in line with the normal standard care for all participants. Post-operatively participants will make three additional visits to clinic at 3, 6 and 12 months, compared to routine follow up. At every visit, participants will complete the PROM questionnaires and undergo clinical assessment, as specified in section 5. Any dislocations or further surgeries will be recorded. All healthcare visits will be recorded, to enable cost analysis. At the 12 month post-operative visit participants will have standardised anteroposterior and lateral X-rays taken. At the 12-month visit, the subset of participants who were selected to undergo gait analysis pre-operatively will undergo repeat gait analysis. The subset of 50 patients who were randomly selected to undergo a second pelvic CT scan, will have this scan performed at the 12-month visit. Any patients in the study who do suffer a dislocation will be managed in line with the normal standard care. See sections 8.5 and 8.6 for more detail on visit schedule.

There will also be a third observational arm to the study. When patients are approached in clinic and offered entry into the randomised controlled trial, some patients may decline to take part. These patients will then be offered entry into the third observational arm of the study. This third study arm therefore will consist solely of patients who were approached in clinic but declined to be randomised into the clinical trial.

Patients in the third observational arm will continue in routine care as normal, and will not make any additional study visits. Their demographics will be collected and their pre- and post-operative Oxford hip scores and EQ-5D scores will be collected, as occurs in routine care. This third observational study arm will enable an assessment of whether the cohort who consented to undergo randomisation and enter the two randomised study arms are representative of all patients.

7. PARTICIPANT IDENTIFICATION

7.1. Trial Participants

Trial participants will be male and female adults between 18 and 85 years of age, with a diagnosis of hip OA, post-traumatic OA, inflammatory arthropathy, avascular necrosis, or congenital/developmental hip disease. Their disease is severe enough to warrant total hip arthroplasty (THA). Once recruitment begins, patients meeting the inclusion criteria will be identified at consultant-led outpatient and pre-operative assessment clinics at each participating centre. Patients will be approached during clinic appointments and offered entry into the trial.

7.2. Inclusion Criteria

- Participant is willing and able to give informed consent for participation in the trial
- Male or Female, aged 18 to 85 years at recruitment into trial
- Diagnosed with hip OA, post-traumatic OA, inflammatory arthropathy, avascular necrosis, or congenital or developmental hip disease, avascular necrosis of the hip
- Listed for total hip arthroplasty at one of participating centres
- Female participants of child bearing potential must be willing to ensure that they use effective contraception during the trial
- Participant is fit to undergo total hip arthroplasty based on consultant anaesthetist review
- In the Investigator's opinion, is able and willing to comply with all trial requirements
- Willing to allow his or her General Practitioner and consultant, if appropriate, to be notified of participation in the trial

7.3. Exclusion Criteria

The participant may not enter the trial if ANY of the following apply:

- Inability to provide informed consent
- Previous surgery to the ipsilateral hip
- Significant co-morbidities that would make follow up difficult or uncomfortable
- Scheduled elective surgery or other procedures requiring general anaesthesia during the trial
- Pregnancy

8. TRIAL PROCEDURES

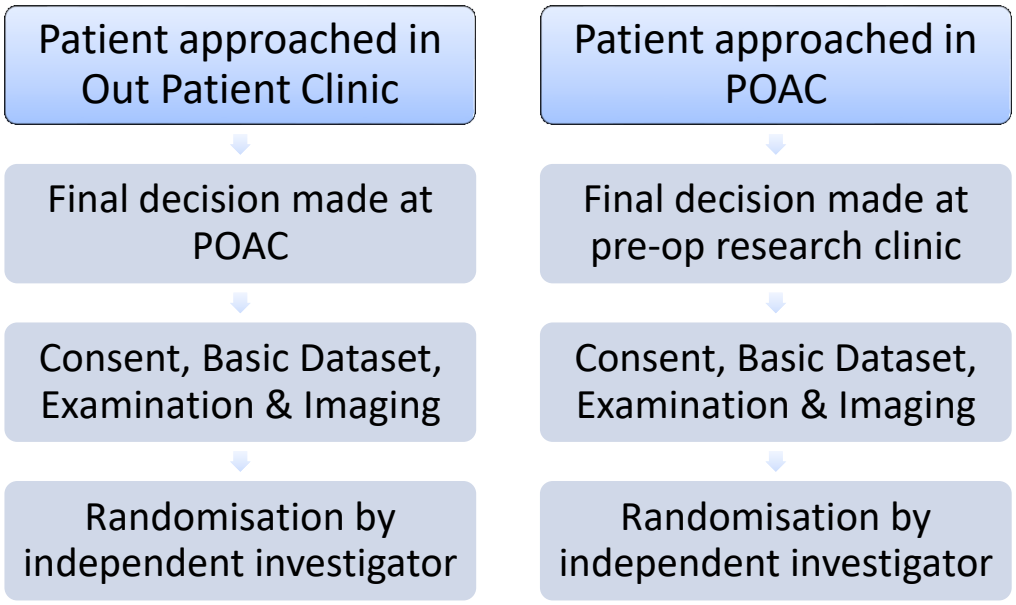
8.1. Recruitment

Once recruitment begins, potential participants will be identified at consultant-led outpatient and pre-operative assessment clinics at each participating centre. During clinic appointments, orthopaedic surgeons will introduce the study to patients and refer them to a member of the study team, who will also be present in clinic, to discuss the study in detail and provide any further information requested. Patients will be asked to "opt-in" if they are provisionally interested in participating. If patients agree to "opt-in" they will be asked to sign the opt-in form and leave their contact details on a document detailing their agreement and permission to being contacted by a member of the research team to further discuss the study. Signing this document does not confer consent to participating in the study, simply to being contacted to further discuss the study. If potential participants do not wish to opt-in and are not interested in participating in the randomised study, they will be offered entry into the third observational study arm at this point.

After signing the "opt-in" document, potential participants will then be given a minimum of 48 hours to consider the study information and to discuss the study with their family and GP should they desire. Potential participants will then be contacted by telephone. At this time, any further questions will be addressed, and if the individual would like to participate in the study, a consent visit will be arranged for consenting. It is proposed that these appointments will occur within four weeks of the initial approach. If when contacted by telephone potential participants decline to take part in the randomised study, they will be offered entry into the third observational study arm.

At the consent appointment participants will meet with a member of the research team again to discuss the process and to discuss the study further. The surgeon may also attend this visit. It will be clearly stated that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal. The research nurse obtaining consent will be suitably qualified and experienced. A copy of the signed Informed Consent will be given to the participants and the original signed form will be retained at the study site.

After participants have consented to take part in the randomised study, randomisation will occur and the baseline assessment visit will be scheduled. For participants in the third observational arm of the study, they will continue in routine care as normal with no further study visits. Their demographic data and pre- and post-operative OHS and EQ5D, collected routinely, will be recorded for the study.



8.2. Screening and Eligibility Assessment

After consent to take part has been given the following information will be collected about each patient and recorded on the CRFs:

- Demographics
    - Date of birth, gender, BMI, height, weight, and smoking status
- Medical history
    - Details of history of disease or surgical intervention in the following systems: inflammatory joint disease, previous surgery, previous joint infections, contralateral hip disease
- Concomitant medication
    - All over the counter or prescription medication

The maximum time between screening and randomisation is one year.

8.3. Informed Consent

The participant must personally sign and date the latest approved version of the Informed Consent form before any trial specific procedures are performed.

Written and verbal versions of the Participant Information and Informed Consent will be presented to the participants detailing no less than: the exact nature of the trial; what it will involve for the participant; the implications and constraints of the protocol; the known side effects and any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the trial at any time for any reason without prejudice to future care, without affecting their legal rights and with no obligation to give the reason for withdrawal.

The participant will be allowed as much time as wished to consider the information, and the opportunity to question the Investigator, their GP or other independent parties to decide whether they will participate in the trial. Written Informed Consent will then be obtained by means of participant dated signature and dated signature of the person who presented and obtained the Informed Consent. The person who obtained the consent must be suitably qualified and experienced, and have been authorised to do so by the Chief/Principal Investigator. A copy of the signed Informed Consent will be given to the participant. The original signed form will be retained at the study site.

8.4. Randomisation, blinding and code-breaking

Following written informed consent and confirmation of eligibility, all patients will be randomised into the study. Patients will be allocated a study number and will be randomised on a 1:1 basis to receive one of the two treatment options. During study recruitment, 50 participants (25 in each study arm) will be randomly selected to undergo gait analysis. At the end of study recruitment, 50 participants will be randomly selected from arm 2 (OPS arm) of the study cohort to have a second CT scan, which will be performed at 12-months post-operatively.

Randomisation will be performed using an automated computer-generated minimisation system through the Oxford Surgical Interventional Trials Unit to age (<40, ≥40 and <65, or ≥65), and gender. This process will occur centrally in Oxford and be overseen by the trial coordinator. Investigators at other sites will contact the site in Oxford to get each participant's randomisation allocation. Patients will be blinded as to which arm of the trial they have been allocated. The Oxford trial coordinator, the operating surgeon and the theatre staff will be unblinded and aware of which treatment arm the patient is in. The post-operative care team will remain blinded.

The Oxford trial coordinator will retain a full list of all recruited patients, their anonymous code number, and the treatment arm they have been allocated to. Trial coordinators at other sites and all operating surgeons will have access to a partial list, containing the same information on patients recruited at their own site only.

They will be the only people with access to this list. They will not have any role in collecting, reviewing, or interpreting post-operative data. Members of the research team who will be post-operatively assessing patients clinically, reviewing images or collecting and interpreting PROMs data will be blinded to patient allocation.

We do not anticipate a situation where code breaking will be required because the surgeons are not blinded to which arm the patients are in.

8.5. Baseline Assessments

The follow assessments will be carried out at the baseline appointment:

Validated Patient Reported Outcome Measures (PROMs) Questionnaires:

Oxford hip score (OHS); International Hip Outcome Tool-33 (iHOT33); Hip and Groin Outcome Score (HAGOS); Pain Detect score; University of California, Los Angeles (UCLA) Activity Score; EuroQoL-5D score (EQ5D); Harris hip score (HHS)

CT scan:

CT imaging of pelvis

X-Ray:

Dynamic series of x-rays of pelvis and hip

Pregnancy test

Clinical assessment:

Examination of range of movement; examination of fixed flexion deformity; examination of leg length discrepancy

Subset of 50 participants (25 in each arm) will undergo gait analysis. These participants will be randomly selected from each study arm. Participants with comorbidities that significantly affect their gait will be excluded from gait analysis.

Assessors of all imaging, PROMs, and clinical assessment will be blinded to which arm of the trial patients were in.

8.6. Summary of Visits

Routine clinical practice will take priority and the study timetable has been drawn up to allow the study procedures to fall within current surgical waiting times. Taking part in the study, therefore, will not delay or expedite treatment. Below is a summary of what will take place at each visit:

Visit 1: Consent visit

- Scheduled within 4-6 weeks of when potential participants are initially approached
- Consent form discussed and signed
- Following this visit, participants will be randomised into one of the two study arms
- If patients decline entry into the study, they will be offered entry into the 3rd observational arm of the study

Visit 2: Baseline assessment visit

- Scheduled for soon after consent visit
- Baseline assessments (detailed in section 8.5) completed

Visit 3: Gait Analysis Visit (subset of patients only)

- Scheduled for same day as or soon after baseline assessment visit (because scheduling CT scan and gait analysis on the same day may not be possible)

Visit 4: Study intervention

- Scheduled for 6-8 weeks after the baseline assessment (Thus patients will have a wait for surgery of approximately 3 months after entry into the study, which is in line with the current surgery waiting time in the participating centres.) Participants will undergo THA surgery in accordance with their randomisation allocation.
- Operative details to be collected:

- Date of surgery
- Randomisation group
- Name of consultant in charge of care
- Grade of lead surgeon
- Grade of assistant surgeons
- Operative side
- Duration of surgery
- Estimated blood loss
- Surgical approach
- ASA grade
- Use of systemic prophylactic therapy (antibacterial and anticoagulant)
- Anaesthesia type
- Acetabular and femoral bone quality
- Whether there was an attempt to correct leg length (if so, what amount attempted and achieved)
- Occurrence of per-operative complications
- Ease of reduction
- Acetabular grafting performed
- Femoral grafting performed
- Details of hip prosthetic components used – including information from device labels
- Other comments on operation

Visit 5: 3-month post-operative visit

- Completion of PROM questionnaires
- Clinical assessment (to include full examination of hip joint and assessment of leg length discrepancy)
- Recording of dislocations, further surgeries or adverse events
- Recording of details of any other healthcare usage by the participants (for cost analysis)
- Review of medical records and recording of any significant events

Visit 6: 6-month post-operative visit

- Completion of PROM questionnaires
- Clinical assessment (to include full examination of hip joint and assessment of leg length discrepancy)
- Recording of dislocations, further surgeries or adverse events
- Recording of details of any other healthcare usage by the participants (for cost analysis)
- Standardised anteroposterior and lateral x-rays taken
- Review of medical records and recording of any significant events

Visit 7: 12-month post-operative visit

- Completion of PROM questionnaires
- Clinical assessment (to include full examination of hip joint and assessment of leg length discrepancy)
- Recording of dislocations, further surgeries or adverse events
- Recording of details of any other healthcare usage by the participants (for cost analysis)
- Standardised anteroposterior and lateral x-rays taken
- Gait analysis performed on the subset of 50 participants randomly selected pre-operatively

- Subset of 50 participants will undergo a post-operative CT scan. These 50 participants will be randomly selected from arm 2 (OPS arm) of the study cohort.
- Review of medical records and recording of any significant events

Completion of this visit marks the end of trial participation

Reasonable travel expenses to the hospital for the additional appointments for the study purposes will be reimbursed.

9. DESCRIPTION OF PROCEDURES

THA will be performed under general anaesthesia or spinal anaesthesia. The surgical technique will be standardised across all sites. All surgeons operating within the trial perform in excess of 60 hip arthroplasties annually. THA will be performed via anterior, antero-lateral, lateral or posterior approach. The study will use the Corin Trinity shell system for the acetabular system. The study will use all compatible Corin stem implants (MiniHip, TriFit, MetaFix and TaperFit) for the stem implant. All head and stem sizes will be included in the trial. All implants will be supplied by Corin Ltd. Pre-operatively all patients (both arms) will undergo dynamic imaging (computer tomography scanning and X-ray films) of their pelvis and hips.

Arm 1: Best practice total hip arthroplasty (THA) with conventional templating

An antero-posterior view radiograph of the pelvis (with legs positioned in 15^{o} internal rotation) and a lateral view radiograph of the hip are required for conventional templating. The radiographs will be examined pre-operatively and appropriately sized cup and stem implants selected for each patient. Intra-operatively, the surgeon may select a different sized implant to that predicted by templating if clinically appropriate.

Arm 2: Best practice total hip arthroplasty (THA) with Corin OPS to guide templating

Patients in the intervention arm will undergo an identical total hip arthroplasty operation. The difference will be the templating procedure used to accurately align the acetabular cup.

The pre-operative dynamic imaging of patients in the OPS arm will be used to calculate the personalised target orientation of the acetabular cup in each patient. A unique physical guide is then created for each patient, which facilitates the accurate positioning of the prosthetic acetabular cup. The guide is a model that fits precisely into the acetabular fossa.

At the appropriate step during the operation, the acetabular fossa is cleared of the fat pad and remnants of the ligamentum teres. Cartilage is removed from areas within the acetabulum where the arms of the guide will sit. The guide is then placed accurately into the acetabular fossa, using guide-holding forceps. Five reference markings on the model assist with accurately locating the guide. Superomedial pressure is applied to ensure it is fully seated within the fossa and rigidly stable. An acetabular laser assembly is then attached to the back of the guide. A pelvic screw is screwed into the bone either around the acetabulum within the incision or percutaneously into the iliac crest. Once the screw is fixed rigidly, a pelvic laser assembly is attached to the back of the pelvic screw. The alignment of the pelvic screw laser is then

adjusted until the laser converges with the laser of the acetabular guide, as projected onto the operating theatre wall or ceiling. The pelvic laser is secured with a dial.

The acetabular laser assembly is then detached from the guide, and the guide is removed from the acetabulum. The pelvic laser assembly is detached from the pelvic screw. The acetabulum is reamed as per the routine technique. The pelvic laser assembly is then reattached to the back of the pelvic screw. Care is taken not to change the direction of the pelvic laser. Next, the acetabular laser assembly is connected to a magnetic impactor adaptor and attached to the back of the prosthetic acetabular cup introducer. The cup is placed in the acetabulum and the orientation is adjusted until the acetabular laser converges with the pelvic laser. The pelvic laser assembly is removed and the acetabular cup is impacted. Note that the pelvic laser assembly can be repeatedly attached and removed to assess alignment during impaction. Once the cup is fully impacted in a satisfactory position, the pelvic screw can be removed, and the operation completed as per the routine technique.

In both arms all intra-operative findings will be recorded on the operation note. Participants will be assessed post operatively by the physiotherapy and medical teams to ensure safety for discharge and when safe patients will be discharged home in line with standard routine care. After discharge, all patients will follow an identical physiotherapy regime, which will follow standard practice after total hip arthroplasty.

Patients receiving the THA operation will have either a general anaesthetic or an epidural anaesthetic. The decision of which type of anaesthetic is given is up to the clinical judgement of the anaesthetist, and will be based on the patient's overall health status. For patients undergoing epidural anaesthesia, a large sterile sheet drape will be placed vertically at the level of the patient's abdomen during surgery. This is to both (1) keep the surgical field sterile and (2) completely obstruct the patient’s view of the surgical field and the surgeon, which could prove distressing to the patient during surgery. Furthermore, patients will be given strong relaxant medications during surgery, making them less aware of what is taking place. The patients who undergo epidural anaesthesia therefore will not be able to tell what type of templating is taking place, and so blinding will remain in place.

9.1. Discontinuation/Withdrawal of Participants from Trial Treatment

Each participant has the right to withdraw from the trial at any time. In addition, the Investigator may discontinue a participant from the trial at any time if the Investigator considers it necessary for any reason including:

- Pregnancy
- Ineligibility (either arising during the trial or retrospectively having been overlooked at screening)
- Significant protocol deviation
- Significant non-compliance with trial requirements
- An adverse event which requires revision surgery
- Withdrawal of Consent
- Loss to follow up

The reason for withdrawal will be recorded in the CRF.

If the participant is withdrawn due to an adverse event, the Investigator will arrange for follow-up visits or telephone calls until the adverse event has resolved or stabilised.

9.2. Definition of End of Trial

The end of trial is the date of the last clinic visit, at 12 months post-operatively, of the last recruited participant.

10. SAFETY REPORTING

Surgery

All participants will be recruited from a population that are on waiting lists for total hip arthroplasty surgery at one of the participating centres. All procedures will be carried out in accordance with existing practice and therefore participation in the study will not confer any increased risk. Surgical risks are minor and rare but include infection, thromboembolism, persistent pain, bleeding, damage to nerves of blood vessels, stiffness, injuries caused by traction and failure of procedure.

The insertion of the pelvic screw into the pelvis is the additional step in the intervention arm that carries risk. Risks from this part of the procedure would be similar to those of the control arm surgery itself in terms of pain, bleeding, infection, damage to nerves or blood vessels, or failure of procedure. The risk of infection in both procedures is minimised by the use of prophylactic antibiotics. Complications from the surgery will be monitored as per each NHS trust protocol for routine postoperative care. This involves regular monitoring by nursing staff and doctors for evidence of postoperative complications whilst the participant is an inpatient, and at every follow up visit when the patient is an outpatient. Wound sites will be checked for evidence of infection, collections, or failure to heal, observations will be monitored for signs of infection or complication, and blood tests will be monitored for evidence of bleeding, infection, or electrolyte imbalance. The patient will only be discharged from in-patient care once both medical and physiotherapy teams agree that the patient is safe for discharge as per standard postoperative protocol.

10.1. Definition of Serious Adverse Events

A serious adverse event is any untoward medical occurrence that:

- results in death
- is life-threatening
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity
- consists of a congenital anomaly or birth defect.

Other ‘important medical events’ may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences.

NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

10.2. Reporting Procedures for Serious Adverse Events

A serious adverse event (SAE) occurring to a participant should be reported to the REC that gave a favourable opinion of the study where in the opinion of the Chief Investigator the event was 'related' (resulted from administration of any of the research procedures) and 'unexpected' in relation to those procedures. Reports of related and unexpected SAEs should be submitted within 15 working days of the Chief Investigator becoming aware of the event, using the HRA report of serious adverse event form (see HRA website). Any adverse event considered to be related to any devices supplied by Corin shall be submitted to Corin via https://vigilance.coringroup.com/vigilance-form/.

11. STATISTICS

11.1. The Number of Participants

The study's aim is to determine whether the Corin OPS system reduces dislocation rate, compared to standard surgical technique and templating. A literature review found that the dislocation rate after THA was 5.0%[11,17,18]. A clinically significant difference of interest of 4.5% will be used in this study, meaning the required dislocation rate in the OPS group is <0.5%. We performed a power calculation, with α significance of 0.05 and power of 0.8, which gave a required sample size of 414 participants. Accounting for a dropout rate of 10%, this gives a total requires sample size of 460, with 230 participants in each arm.

The first 100 participants recruited will be entered into an internal pilot study. The internal pilot study will study the rate of recruitment of participants and analyse whether completion of recruitment of all patients is feasible within our time limits. If the internal pilot study shows that completing the study is unfeasible, then the full trial will be terminated. The internal pilot study will allow calculation of a provisional dislocation rate (the primary outcome) in the control arm of the study. The rationale for this is that the control arm participants may have a different dislocation rate to that found in our literature review. Using the dislocation rate in the internal pilot study and the minimum clinically significant difference of interest, we will re-calculate the sample size require to fully power the full study. We expect, therefore, that the full study sample size may change by 5% either way from our projected sample size of 476 participants. However, if the size of the cohort increases by more than 5% (to above 500) we may need to re-approach the funder to enable us to recruit additional participants.

The subgroup of 50 participants receiving gait analysis pre-operatively and at 12-month post-operatively will include 25 participants from each study arm. The sample size of 50 is of sufficient size to give detailed information. Analysis on a larger group is not possible due to gait laboratory capacity constraints.

The subgroup of participants receiving a 12-month post-operative CT scan will include 50 participants from the OPS arm. The position of the implant compared to the planned position will be analysed. The sample size of 50 is of sufficient size to give detailed information. Analysis on a larger subgroup is not possible due to financial constraints.

11.2. Description of Statistical Methods

The statistical analysis is the responsibility of the NDORMS OSIRIS Trial Statistician. A full statistical analysis plan will be written and agreed by the Trial Steering Committee before any analyses are undertaken, and all reporting will follow the CONSORT reporting guidelines.

All primary analyses will follow an 'intention to treat' (ITT) principle, with all participants included in the analyses based on the treatment arm to which they were initially randomised, regardless of their compliance with the protocol.

The analysis of this study will be performed after all participants have completed their 12-month post intervention assessment. Data will also be analysed with respect to health economics.

The primary outcome of dislocation rate will be calculated in each group. Data will be examined for distribution and the most appropriate statistical test used. If the data are normally distributed, a two-sample t-test to compare groups may be the most appropriate. Multivariate linear regression analysis will be used to identify differences between the treatment groups using separate two-way comparisons (best practice THA surgical technique and templating versus best practice THA surgical technique with OPS-guided templating). The model will be adjusted for relevant baseline characteristics.

11.3. The Level of Statistical Significance

All hypothesis testing will be performed at the two-sided 5% level of significance.

11.4. Criteria for the Termination of the Trial

The trial will be terminated at the one year follow up for all participants, or if any serious adverse outcome related to use of the pelvic screw or the laser assembly system were to become apparent during the trial, the leading members of the trial would meet to determine the nature of the outcome and decide upon the need to terminate the trial.

11.5. Procedure for Accounting for Missing, Unused, and Spurious Data

Missing or spurious data will be fully investigated as to ascertain the reason. The PI will then decide whether the participant(s) whose data are missing should continue to be followed. All missing, unused or spurious data will be accounted for in any analyses

11.6. Inclusion in Analysis

All randomised participants will be included in the analyses. If a participant is unblinded, then only information gathered on the participant prior to unblinding will be used in the analysis.

11.7. Procedures for Reporting any Deviation(s) from the Original Statistical Plan

A full statistical analysis plan will be written and agreed by the Trial Steering Committee before any analyses are undertaken, and all reporting will follow the CONSORT reporting guidelines. Any deviation from this will be reported in the final report and accounted for in future trial planning and analysis.

12. DATA MANAGEMENT

12.1. Access to Data

Direct access will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections.

12.2. Data Recording and Record Keeping

Members of the trial team will be able to access the digital or paper records of patients enrolled in the trial for data collection. Radiological images will be downloaded from the image acquisition equipment or PACS onto DVDs for upload onto study computers for analysis. All personal data for patients including addresses, contact numbers and email addresses will be held in paper records and electronically. Data will be anonymised at the earliest practical point. Thenceforth the participants will be identified by a unique trial specific number.

University desktop and laptop computers will be used to analyse data but they will not be used to store patient identifiable data. Participants will be identified by means of unique and anonymous code numbers within the trial database and this will be encrypted. The trial coordinator, who will be unblinded, will retain a list of patients, their anonymous code number, and the treatment arm they have been allocated to. They will be the only person with access to this list. Electronic data that contains identifiable data will be retained on password protected computers at the study sites and data will be backed up using encrypted external hard drives stored with imaging DVDs in a locked cabinet in the Botnar Research Centre (BRC). The BRC is an alarmed facility accessed only by authorized personnel using swipe card or proximity access security systems.

If the clinical condition of a participant necessitates breaking the code, then the trial coordinator will be responsible for breaking the code in this situation. If they are unavailable then the surgeon who performed the procedure will be required to break the code. Any request to break the code, and the act of breaking the code, will be documented for time, date, requester, and person informed. The trial coordinator and surgeon who performed the procedure, who will be unblinded, will retain a list of patients, their anonymous code number, and the treatment arm they have been allocated to. They will be the only people with access to this list. In the event of a need to code-break, the trial coordinator will be responsible for accessing this list to determine treatment allocation and will inform the principal investigator of this.

13. QUALITY ASSURANCE PROCEDURES

The study may be monitored, or audited in accordance with the current approved protocol, GCP, relevant regulations and standard operating procedures.

14. OTHER ETHICAL CONSIDERATIONS

No randomized trial has been performed to investigate the efficacy of the OPS system in reducing dislocation rates after total hip arthroplasty. In light of this absence of evidence, we believe the best method to identify if the use of this system will improve outcomes for patients is a randomized controlled trial to compare the use of OPS in THA with conventional templating in THA.

In the NHS when performing total hip replacement, a consultant surgeon is able to choose which prosthetic femoral stem and acetabular cup to use based on their expert opinion, as long as the implants are approved for use in the UK. The Corin femoral stem options (MiniHip, TriFit, MetaFix and TaperFit) and acetabular cup (Trinity shell system) that will be used in this study are CE marked and widely used across the UK. A range of sizes are available to suit all anatomical morphologies. Patients will only be included in this study and receive the Corin implants if their surgeons approve that use of the Corin implants is suitable.

The duration of the surgical procedure for participants in the OPS arm of the study is likely to be longer compared to routine care. This is because of the added steps required in positioning the acetabular shell during the operation. Based on previous experience in the use of Corin OPS for THR, the average increased duration of surgery is 15 minutes, from 70 minutes to 85 minutes. This increase in duration of surgery is within safe limits and will not place the participants at significant risk.

The radiation exposure will be greater for all participants in the study, compared to if they underwent THR with routine care. The additional radiation exposure has been reviewed and risk assessed by a Consultant Radiologist and a Medical Physics Expert. The additional radiation dose was approved. The additional risk will be fully explained to patients at recruitment.

Participation in this trial may lead to more follow-up visits than routine care in order to collect the outcome measurements. This may be considered an inconvenience to patients and accordingly we will make this clear during the consent process prior to enrolment. The more frequent visits have a potentially beneficial effect giving patients greater opportunities to ask any questions they may have and also to pick up any complications that may arise following surgery.

14.1. Declaration of Helsinki

The Investigator will ensure that this trial is conducted in accordance with the principles of the Declaration of Helsinki.

14.2. Guidelines for Good Clinical Practice

The Investigator will ensure that this trial is conducted in accordance with relevant regulations and with Good Clinical Practice.

14.3. Approvals

The protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to an appropriate Research Ethics Committee (REC), HRA, regulatory authorities, and host institutions for written approval.

The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

14.4. Reporting

The CI shall submit once a year throughout the clinical trial, or on request, an Annual Progress Report to the REC, HRA (where required), host organisation and Sponsor. In addition, an End of Trial notification and final report will be submitted to the REC, host organisation and Sponsor.

14.5. Participant Confidentiality

The trial staff will ensure that the participants' anonymity is maintained. The participants will be identified only by a participant ID number on all trial documents and any electronic database, with the exception of the CRF, where participant initials may be added. All documents will be stored securely and only accessible by trial staff and authorised personnel. The trial will comply with the Data Protection Act, which requires data to be anonymised as soon as it is practical to do so.

14.6. Expenses and Benefits

Reasonable travel expenses for any visits additional to normal care will be reimbursed on production of receipts, or a mileage allowance provided as appropriate.

15. FINANCE AND INSURANCE

15.1. Funding

All research facilities required are located and available at the Nuffield Orthopaedic centre site. All surgical facilities are available and in place, located at the sites taking part in the study. The facilities would be in use for the scheduled arthroplasty surgery regardless. Corin Ltd will supply all equipment and training required for the use of the OPS system. Corin Ltd has supplied £488,280.44 to fund the running of the trial for three years. If the internal pilot shows the study is unfeasible, the study will be terminated early pending mutual agreement from both parties.

15.2. Insurance

The University has a specialist insurance policy in place, which would operate in the event of any participant suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, at Lloyd's of London). NHS indemnity operates in respect of the clinical treatment that is provided.

16. PUBLICATION POLICY

Reporting will follow the CONSORT statement protocol for reporting RCTs. The investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authors will acknowledge the funders of the study. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged.

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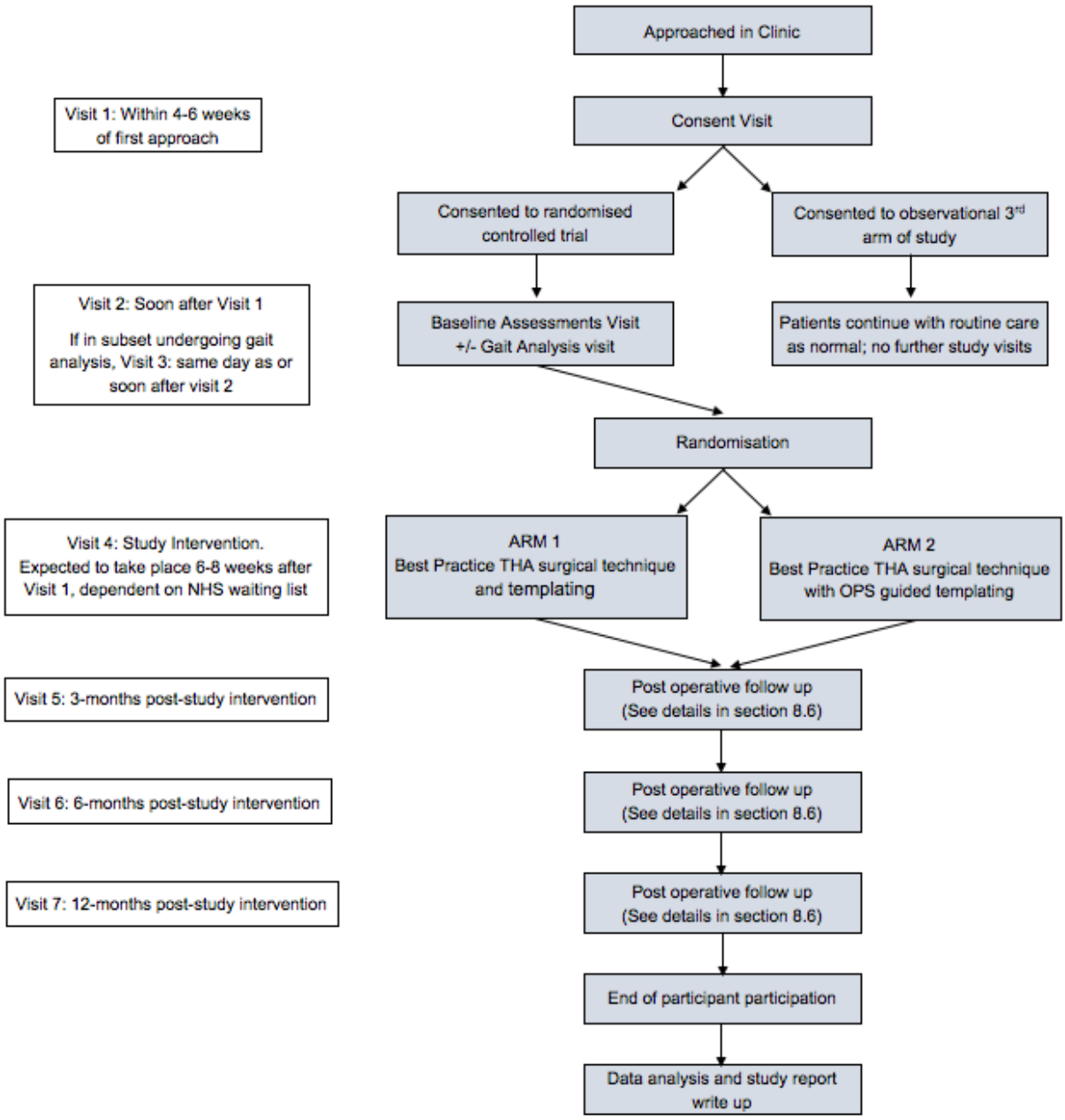
18. APPENDIX A: TRIAL FLOW CHART



19. APPENDIX B: SCHEDULE OF PROCEDURES

	Approach in clinic	Consent visit	Baseline visit	Intervention	3 months	6 months	12 months
Explain study	X	X					
Opt-in form	X						
Eligibility assessment		X					
Informed consent		X					
Collect demographics & medical history details		X					
Clinical examination			X	X	X	X	X
Operative details recorded				X			
CT scan			X				X*
X-rays			X				X
PROMs & HHS			X		X	X	X
Gait analysis			X#				X#
Health economics							X
Adverse events (as reported)				X	X	X	X

*Only in a select subgroup of patients (see section 8.6)

#Only in a select subgroup of patients (see section 8.5)

20. APPENDIX C: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made