PROTOCOL

Robotic Arthroplasty: a Clinical and cost-Effectiveness Randomised controlled trial for Hips (RACER-Hip)

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TRIAL SUMMARY

Trial Title	Robotic assisted Arthroplasty: a Clinical and cost-Effectiveness Randomised controlled trial for Hips (RACER-Hip)
Short Title	Robotic Assisted Hip Arthroplasty
Trial Design	Pragmatic, multi-centre, patient-assessor blinded randomised controlled trial with health economic evaluation
Trial Participants	People with osteoarthritis undergoing total hip replacement
Planned sample size	378
Intervention	Robotic assisted THR, with preoperative CT imaging
Control	Conventional THR surgery, with preoperative CT imaging
Follow-up Duration	Primary outcome: 12 months Secondary timepoints: six weeks, three months, six months, one, two, five and 10 years.
Planned Trial Period	From: 01/07/2021 to 31/12/2024 for 42 months (note: long-term follow-up from 01/01/2025 planned through to 30/06/2033)
Source of Funding	Trial funded by the NIHR Health Technology Assessment (HTA) programme. Stryker (USA) will fund consumables, pre-operative CT costs and 10 minutes of theatre time, according to contractual arrangements. They will have no involvement in the design, delivery or reporting of the study.
Primary Objectives	*Clinical effectiveness:* To compare robotic-assisted THR against THR performed with conventional surgical instruments on the patient-reported Forgotten Joint Score 12-item scale, 12 months after surgery. *Cost effectiveness:* To determine the cost-effectiveness of robotic assisted THR compared to conventional THR in a UK NHS setting.
Secondary Objectives	To compare differences in intra-operative blood loss, operative time, average pain in the first three days after surgery, time to hospital discharge (hours) and total analgesic use between groups. To compare, between groups, the Forgotten Joint Score (pain and function), Oxford Hip Score, health-related quality of life (EQ-5D-5L), participant satisfaction, surgery related adverse events and implant survival at six weeks (HQoL only), three, six and 12 months; plus, two, five and 10 years following surgery.
Objectives for Process & Fidelity Measures	To compare post-operative component position at three months using CT and x-rays, and robot-derived alignment (robotic group only) To evaluate the uptake and adherence to rehabilitation within the trial

LIST OF ABBREVIATIONS/GLOSSARY

Abbreviation	Explanation
AE	Adverse Event
BOA	British Orthopaedic Association
CI	Chief Investigator
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CRN	Clinical Research Network
CT	Computed Axial Tomography
DMC	Data Monitoring Committee
EME	Efficacy and Mechanism Evaluation, an NIHR/MRC research funding programme
EQ-5D	EuroQol five-domain health utility measure
EQ5D-5L	EuroQol five-domain health utility measure (five level)
FJS	Forgotten Joint Score
GCP	Good Clinical Practice
HES	Hospital Episode Statistics
HTA	Health Technology Assessment, an NIHR research funding programme
IRMER	Ionising Radiation (Medical Exposure) Regulations
IP	Intellectual Property
IRAS	Integrated Research Application System
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trial Number
MCID	Minimal Clinically Important Difference
MD	Mean Difference
MRC	Medical Research Council
MRI	Magnetic Resonance Imaging
mSv	Millisievert, a measure of radiation dose
NHS	National Health Service
NICE	The National Institute for Health and Care Excellence
NIHR	The National Institute for Health Research
NJR	National Joint Registry
NRS	Numerical Rating Scale
OHS	Oxford Hip Score
OMERACT	Outcome Measures in Rheumatology

PI	Principal Investigator
PIC	Participant Identification Centre
PIS	Participant Information Sheet
PPI	Patient & Public Involvement
PROMs	Patient Reported Outcome Measures
PROSPERO	International prospective register of systematic reviews
HRQoL	Health-related Quality of Life
QALY	Quality Adjusted Life Year
RCT	Randomised Controlled Trial
RDS	Research Design Service
REC	Research Ethics Committee
R&D	Research and Development
SAE	Serious Adverse Event
ScAP	Scottish Arthroplasty Project
SIV	Site Initiation Visit
SoECAT	Schedule of Events Cost Attribution Template
SOP	Standard Operating Procedure
SPM	Senior Project Manager
TC	Trial Coordinator
TM	Trial Manager
THR	Total Hip Replacement
TMG	Trial Management Group
TSC	Trial Steering Committee
UHCW	University Hospitals Coventry and Warwickshire
UNTRAP	University/User Teaching and Research Action Partnership
VA	Versus Arthritis
VAS	Visual Analogue Scale
WCTU	Warwick Clinical Trials Unit

1. BACKGROUND

1.1 Total hip replacement surgery

Although total hip replacement (THR) can be very successful for most people, a proportion have some long term persisting pain or functional restriction after surgery and one in ten people report no measurable improvement in pain. (1-4) There is a pressing need to improve patient outcomes after THR surgery.

Robotic-assisted THR surgery may allow more precise and consistent intraoperative surgical techniques, and component (implant) position and may be a promising approach to reduce long term problems after THR.

Conventional THR typically involves a single incision to expose the diseased hip joint and the femoral head (ball) is surgically removed and worn cartilage and bone is excised from the acetabulum (socket). A new artificial socket is sized and inserted. After hollowing out the femur, a long metal stem is also sized and inserted with a new artificial head. The size and position of these components before final fixation is determined by the surgeon. The wound is then closed and a single dressing applied. Before surgery estimates of the size and position for the components are typically planned (templated) based on plain pelvis x-rays.

In robotic assisted THR, a robotic arm constrains preparation of the bone and sizing and insertion of the components to a pre-programmed three-dimensional template following detailed CT scans and plain x-rays before surgery. This template is generated by engineers working for the robotic company in collaboration with the surgeon before the surgery. At the time of surgery small additional incisions are required over the pelvis to allow insertion of pins which hold markers (arrays) so the robot can calibrate and orientate itself correctly.

MAKO is currently the robotic assisted hip replacement system used most frequently within the NHS (MAKO, Stryker, USA) – see figure 1. Whilst other robotic-arm systems are becoming available, their development has been hampered by Stryker holding many of the key patents. There are currently 850 MAKO robots worldwide; 25 used in the UK for hip and knee joint replacement surgery.

Figure 1: The MAKO robot. The surgeon moves it into the surgical field after exposure of diseased join and the robot controls the preparation and insertion of the implants

Robotic assisted total hip replacement (THR) surgery has increased rapidly over recent years. Expensive systems are being introduced into the NHS and ‘sold’ to the press and public as innovative best practice with little evidence that it is a clinically superior, or cost-

effective, alternative to conventional surgery.(5, 6) NHS centres are investing in robotic assisted hip replacement technology at great cost; robotic machines cost £1million each or >£120K per annum in hire costs, additional consumables (approximately £300 per patient) and pre-operative Computed Tomography (CT) scans to plan surgery (approximately £100 per scan). If robotic assisted procedures are not worthwhile, their use should be stopped and these funds should be redirected to care elsewhere in the NHS.

With 106,000 THRs performed in the UK in 2018 and increasing annually, establishing the clinical and cost effectiveness of robotic assisted hip replacement is critical.(7)

1.2 Existing knowledge

A 2018 systematic review of robotic assisted hip replacement found three randomised controlled trials (RCT) (total N=351) from Japan and South Korea, all of low/very low quality evaluating robotic technology no longer in use.(8) All three used the robot for a small part of the procedure (preparing the femur only) and not for component insertion. Two trials were completed >15 years ago. A meta-analysis of these three trials found a lower rate of intra-operative complications including femoral fractures (OR: 0.12, 95% CI: 0.05 to 0.34) and more precise component placement as measured on postoperative imaging (OR: 5.64, 95% CI: 4.10 to 7.74). Clinical markers such as leg length discrepancy (SMD: −0.24, 95% CI: −0.61 to 0.12 measured radiologically) and functional outcome (SMD: 0.12, 95% CI: −0.09 to 0.34) were no different between groups.

Two observational studies (N=228 & 98), both from USA, compared the MAKO robotic assisted hip replacement, to conventional THR.(9, 10). Both studies used only radiographic outcomes. Both studies reported statistically significant improvements on radiologically-determined precision of component placement for robotic assisted hip replacement.

There are three registered, ongoing studies of MAKO robotic assisted hip replacement:

i. A UK (Bournemouth) cohort study (NCT03846791) of 100 patients having MAKO robotic assisted hip replacement at a private hospital, to capture surgical complications and hospital readmissions over 12 months.
ii. An industry funded RCT (NCT03891199) in the USA recruiting 40 patients to find out if MAKO robotic assisted hip replacement improves precision of component placement.
iii. An industry funded RCT (NCT04095845) in the UK (UCL, London) recruiting 80 patients to find out if MAKO robotic assisted hip replacement improves precision of component placement at six weeks with some secondary patient reported outcomes over two years.

These studies will not tell us if robotic assisted hip replacement improves patient reported outcomes compared to conventional THR surgery. There are no cost effectiveness studies.

1.3 Importance of the research

This proposal addresses two of the top 10 questions in the James Lind Priority Setting Partnership for hip and knee replacement:(11)

1. What pre-operative, intra-operative, and post-operative factors can be modified to influence outcomes in hip and knee replacement?

2. What are the best techniques to control longer term chronic pain and improve long term function following hip and knee replacement?

Possible causes for persistent pain and poor function after THR include mechanical and/or intraoperative factors such suboptimal component positioning and incorrect implant sizing which can compromise the biomechanics of the replaced hip. These may be improved by undertaking more precise surgery. Leg length discrepancy or inadequate restoration of femoral offset (horizontal distance between the femur and pelvis) have well established associations with chronic pain, worse functional outcome, limping and greater trochanteric pain syndrome.(12-14) Even subtle abnormalities of component position and size can impact on range of motion, muscle function, or provoke chronic tendonitis due to rubbing against the edge of the replacement.(15-17) Poor component position and sizing also risks postoperative complications such as instability (including dislocation), fracture, and the need for revision surgery.(18-20)

Robotic assisted THR may increase precision and consistency of component sizing and position, and it follows that this may ultimately improve pain and function. Any improvements in acute post-surgical pain may also limit progression to chronic pain.(21, 22) shorten the hospital stay and reduce NHS costs.(32) There could be other cost savings, for example, 16% of successful clinical negligence claims following THR in the NHS are for leg length discrepancy, averaging £112,000 each.(23) It is unclear whether robotic assistance surgery improves clinical outcomes, especially to such a degree that their substantial costs would be offset by the savings.

There is also a potential for harm from robotic assisted surgery, whether from longer surgical times, pain or infection from placement of marker pins, radiation exposure from additional preoperative CT scans and plain x-rays or other unanticipated events which may occur when new technologies are implemented.

Preoperative imaging and planning

Use of the robot requires **pre-operative planning (templating)** using a CT scan as well as a series of up to three plain radiographs of the lower back and pelvis to determine the optimum size and position of the components. This raises the question as to whether such detailed planning itself could influence outcome. In order to ensure participant blinding and isolate only the effects of the robotic intervention all participants will have detailed CT based planning in both arms. Performing the CT in both arms is needed to answer the core question of whether the robotic assisted surgery improves clinical outcomes. If a more pragmatic study design were utilised, comparing planning and robotic delivery against conventional surgery without planning, then it might be concluded that the planning was responsible for any difference in outcome. On this basis, we have concluded that the only way to answer the important and central question of whether the use of robot-assisted surgery is clinically and cost effective for total hip replacement, is a study in which the detailed planning process is isolated from the robotic surgery.

1.4 Why this research is needed now

A randomised trial is needed now to ensure this new technology is truly worthwhile for patients and the NHS. A high-quality randomised controlled trial with patient-centred

clinical, and cost effectiveness, outcomes, is required to establish whether robotic assisted THR is superior for patients compared to conventional surgery, and for the NHS, or if it is an unnecessary cost without clear benefit.

More precise, consistent surgical techniques and component position permitted by robotic assisted hip replacement may reduce variation and prevent poor outcomes such as chronic pain, limited function and reducing the risk of disabling complications that can require revision surgery.(8) Revision surgery has substantial complications (e.g. bone loss, fractures and pain), healthcare costs, and is less likely to improve symptoms and function. In 2018, approximately 7000 THRs were revised, at a cost of £70 million (£10,000 for each case). Newer custom revision implants can cost >£20K. A 5% reduction in annual revisions could save the NHS >£3.5 million per year.(7)

There has been a similar growth in the use of robotic assisted total knee replacement surgery. An NIHR-funded RCT (RACER-Knee NIHR 128768) led by Warwick Clinical Trials Unit (WCTU), open to recruitment, is comparing the clinical and cost effectiveness of robotic assisted knee replacement to conventional knee replacement. However, there are fundamental differences in the criteria for surgery, outcomes, side effect profiles, and tolerances to surgical performance between hip and knee replacement that mean the findings cannot be extrapolated from knee to hip. Key stakeholders including the Royal College of Surgeons Robotic and Digital Surgery Group and the British Hip Society have emphasised that findings cannot be extrapolated from the knee or other joints to the hip. They predict that robotic assisted hip replacement will continue to increase, whatever the results of research on robotic surgery in other joints.

1.5 Aims and objectives

1.5.1 Aim

To compare the clinical and cost-effectiveness of robotic assisted THR versus THR undertaken using conventional instruments on health-related outcomes for people with osteoarthritis.

1.5.2 Objectives

Primary objectives

i. To determine if robotic assisted THR improves pain and function at 12 months post-randomisation (measured using the Forgotten Joint Score), compared to conventional THR surgery.

ii. To determine the cost-effectiveness of robotic assisted THR in the UK, compared to conventional THR.

Secondary objectives

i. To compare pain and opioid analgesic use in the first three days after surgery.

ii. To compare duration of surgery, blood loss and time to discharge.

ii. To compare the Forgotten Joint Score, Oxford Hip Score, EQ-5D-5L (at 6 weeks also), pain intensity, satisfaction, serious adverse events related to the operation and implant survival at three, six months, one, two, five and 10 years following surgery.

1.6 Ethical considerations

The trial will be conducted in conformance with the principles of the Declaration of Helsinki and to Good Clinical Practice (GCP) guidelines. It will also comply with all applicable UK legislation and Warwick Standard Operating Procedures (SOPs). All data will be stored securely and held in accordance with current legislation.

In this study, participants in both arms will receive active treatment, the control arm will receive full active care to the same standard received by all patients who undergo THR in the UK. As the surgical planning, implant type and operating surgeon will all be identical between arms, the only difference between the groups will be the delivery of the surgery itself, either with the robotic-arm system or with conventional instruments.
The main ethical issue for this study are that participants will have additional imaging with radiation exposure and half the participants will have up to three small sham incisions to maintain blinding.

The total radiation dose for participants in the study represents a theoretical additional risk of causing cancer of approximately 0.05%, on a baseline risk of 50%. This has been discussed with key stakeholders, including our ten patient advisory group members, who were all very positive and they felt that the benefits of the additional information outweighed the very small risk to participants. We propose that all sites with the aid of a suitably calibrated radiation monitoring device, will need to show that the locally delivered CT and radiograph protocol is equal to or less than our calculated radiation dose before beginning recruitment.

The three small sham incisions are all less than five millimetres each. Blinding in surgical trials using sham or placebo incisions is strongly recommended by the Royal College of Surgeons, where it can be achieved and our patient advisory group also understood the importance of this and supported it.(24, 25) We do not anticipate these challenges which have been carefully considered being a barrier to obtaining ethical approval for this study. A further ethical consideration is our relationship with Stryker. The company has not had, and will not have any involvement in the design, delivery or interpretation of the study in line with NIHR policy. We will have clear contractual agreements to ensure the study is managed fully independently, in line with the NIHR contracts. We have consulted with the company on technical issues related to the delivery of the intervention and have a similar arrangement with Stryker for START:REACTS (NIHR EME, 16/61/18) and RACER-Knee.

1.7 CONSORT

The trial will be reported in line with the CONSORT (*Con*solidated *S*tandards *o*f *R*eporting *T*rials) statement. (26)

1.8 Assessment and management of risk

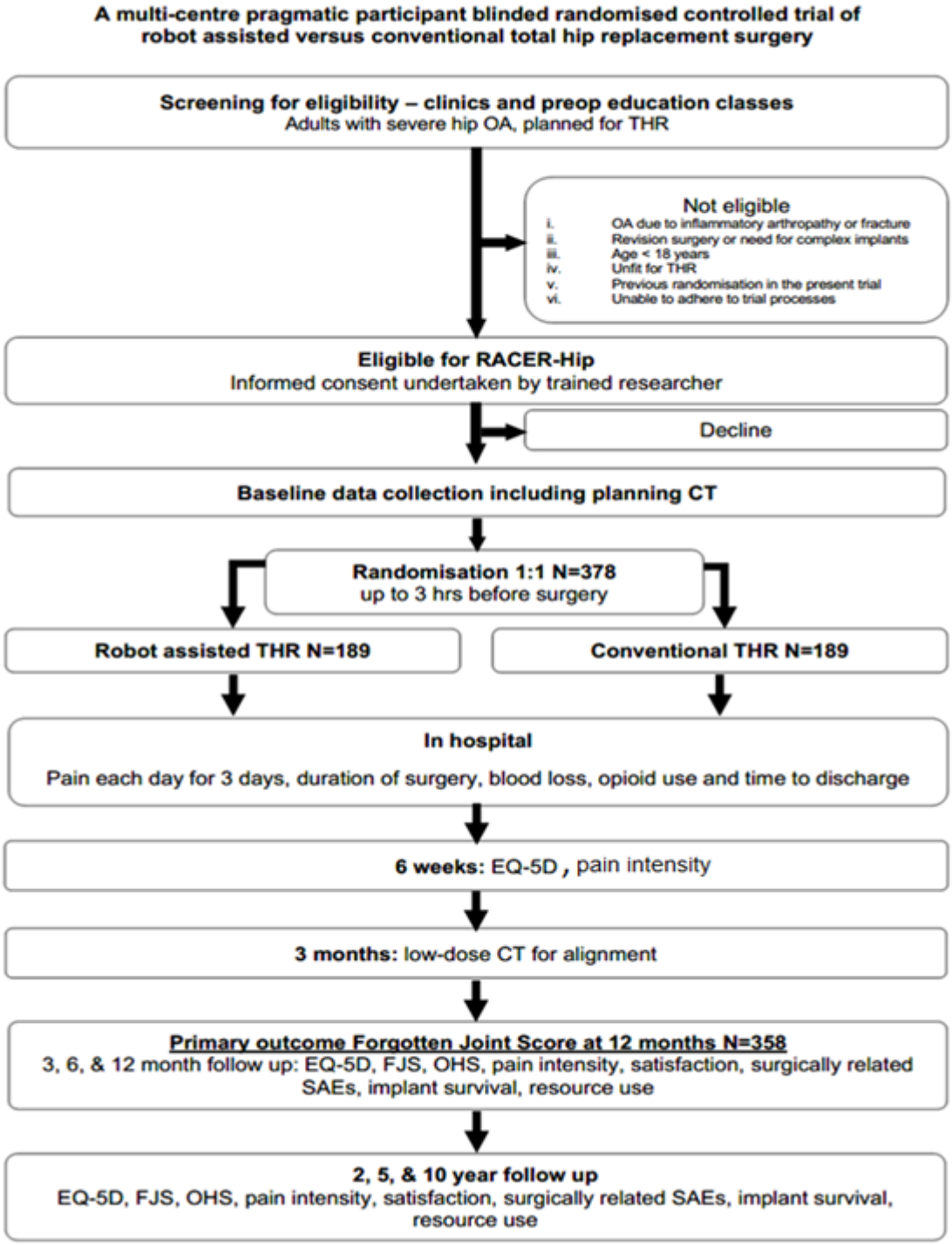
The interventions are both standard interventions, used in the NHS at present, and within their licenced indications. There is a very small additional risk related to the radiation dose (noted above). A risk assessment will be performed according to Warwick Standard Operating Procedures (SOP).

2. TRIAL DESIGN

2.1 Trial summary and flow diagram

RACER-Hip is a multi-centre, patient-assessor blinded, pragmatic randomised controlled trial to assess the clinical and cost-effectiveness of CT-imaging with robotic assisted THR compared to conventional THR in the UK NHS health setting. This is a phase III study according the IDEAL classification for evaluation of surgical interventions.(27)

Figure 1 Trial flow diagram



2.2 Eligibility criteria

Patients are eligible to be included in the trial if they meet the following criteria:

2.2.1 Inclusion criteria

i. **Osteoarthritis of the hip with pain, disability and radiological changes** that in the opinion of the treating clinician, warrants THR

ii. **Conservative therapy has been unsuccessful**, as judged by the treating clinician.**(28)**

2.2.2 Exclusion criteria:

i. **Osteoarthritis due to inflammatory arthropathy or intra-articular fracture,** as judged by the treating clinician

ii. **Revision surgery or need for complex implants,** or any other implants than a standard hybrid construct (Trident Exeter) or uncemented construct (Trident Accolade), as determined by the treating clinician. This includes nickel-free implants as well as those that require a long stem, augments, or custom made devices

iii. **Age < 18 years**

iv. **Unfit for THR, or surgery is otherwise contra-indicated**, for example, current infection

v. **Previous randomisation in the present trial**, i.e. the other hip

vi. **Unable to take part or adhere to trial processes** including prisoners or people unable to communicate or complete questionnaires in English, or people unable to give informed consent.

2.3 Participant identification/screening

Potential participants will be identified by the attending clinical team in intermediate or secondary care clinics, from pre-operative education classes, or from the surgical waiting list. Initial identification will be performed by the normal clinical team, if this is not a hip arthroplasty surgeon or a suitably trained member of clinical staff, a referral will be made to the appropriate clinic to assess eligibility. The 'treating clinician' is the person who sees the patient clinically at that time point and is suitably trained to make that decision. Participant Identification Centre (PIC) sites with access to robotic machines will be considered based on the processes in local sites.

The treating clinician will confirm appropriateness for study eligibility on a CRF based on clinical assessment and standard care pre-operative imaging for that site (this is typically an X-ray but may include MRI or other imaging). Potential participants suitable for inclusion will be given information about the study and invited to discuss the study further with a member of the research team, they will be given adequate time to consider study participation (see below). Depending on the study process at individual sites, information sheets may be posted (or emailed) to potential participants. A member of the local research team will carry out the informed consent process (see 2.4), enrolment and baseline data collection.

As the time between consent and randomisation would typically be three to four months in the NHS due to waiting lists, we will review consent and eligibility with the participant on the morning of surgery to confirm that they are still happy to take part. If baseline

measures are **more than six months old** at the planned operation date, they will be repeated in the month before surgery.

A screening log will be completed remotely at all sites, by site staff using the RACER-Hip online application and exported by the central team monthly for use in management meetings(with any identifiers redacted, except trial numbers for participants). This will include details of the number of people presenting to recruiting clinical teams who are considered suitable for hip replacement, the number meeting eligibility criteria, and the number who consent to enter the study. These data will be used to populate the CONSORT statement in the study report.

2.4 Informed consent

Responsibilities: The local PI retains overall responsibility for informed consent at their site and must ensure that any person listed on the site delegation log with the delegated responsibility to participate in the informed consent process is duly authorised, trained, and competent.
The investigator or their nominee, for example from the research team (research associate or research nurse), will provide both written and/or verbal information to inform the patient of all aspects pertaining to participation in the study. They will also answer any questions that the patient may have concerning study participation. The potential participant will be provided with a study information sheet.

Withdrawal: It will be explained that entry into the study is entirely voluntary and the right of any person to refuse participation without giving reasons will be respected and recorded on the screening log. They may be provided with a contact point where he/she may obtain further information about the trial if requested. The participant will remain free to withdraw from the study at any time without giving reasons and without prejudice to any further treatment (see 2.5.2).

Any new information that arises during the trial that may affect the participant's willingness to continue in the trial will be discussed with the participant and, if applicable, renewed consent will be obtained using an amended consent form.

Lack/loss of capacity: If we become aware that participants who have already had the intervention have lost the ability to consent to follow-up procedures (for example, dementia), and are not expected to regain capacity, we will not perform ongoing follow-up but will interrogate the National Joint Registry (NJR), Scottish Arthroplasty Project (ScAP) and Hospital Episode Statistics (HES) for data on re-operation on the affected hip, and check for adverse events with the GP to follow the process for those participants lost to follow-up. Where a participant has lost the capacity to consent to follow-up, but they may regain capacity (for example, an acute illness causing temporary loss of capacity, or where the potential for recovery is unknown) the follow-up will be delayed until capacity is regained.

Informing GPs:
Participants' GPs will usually be informed by letter that they are taking part in this clinical trial (but will not be told the allocation). Participants may decline for their GP being informed of their participation in the trial involvement by indicating their wishes on the consent form.

Copies of consent: The investigator or their nominee and if applicable the independent witness (as detailed in section2.4.2) must sign and date the consent form. Copies will be posted to the participant, kept by the local investigator team, retained in the patient's hospital record and kept centrally with the CTU for use later when requesting routinely collected date from NHS digital etc.

2.4.1 In-person consent

Potential participants who present themselves to recruiters at the study sites will be given study information and adequate time to consider participation and will be invited to give their consent to become participants in the trial. We have not set a minimum time period to consider as some patients may wish to consent at the time they receive the study information and find additional visits a burden. Even after consent, they will have ample time to consider participation and potentially withdraw whilst on the waiting list for elective surgery, which would typically be three to four months. No participant will provide initial consent for the study on the day of surgery. Additionally, planning CT scans will not be booked or performed until the person has consented.

Potential participants who wish to take more time to consider participation will be given the opportunity to do so and will be offered the option of a further clinic visit, or they will be provided with a consent form to take away to consider. We will ask sites to follow-up these patients with a telephone call for further clarification and to ask if they agree to participate. If the potential participant agrees, they will be asked to return the signed consent form by post in a pre-paid envelope or alternatively a follow-up visit will be arranged, or they can bring the signed consent form with them to the CT appointment (assuming appropriate procedures are in place to check the consent is signed before the CT scan is performed). If consent is returned by post or in person at a future date, a file note will be made to document this, and therefore explain why the countersigned and signed dates differ on the form.

2.4.2 Witnessed verbal consent

Given the low number of NHS sites currently with robotic technology, we anticipate recruitment to sites with large geographical coverage. To avoid multiple journeys and potential travel costs for patients (and associated risks of Covid-19), we will implement a witnessed remote verbal consent process for participants who are unable to attend clinics in person.

A witnessed remote verbal consent will be gained via telephone or any Trust approved online video consultation platforms. The call/video call must be witnessed by a site staff member who will declare that consent was appropriately obtained: study explained, questions answered and time given for participants to make a decision. After remote verbal consent is given, a paper copy of the current consent form will be signed by the clinician delegated to consent and countersigned by the independent witness. A copy of the signed consent form will be given to the patient (via post or in person when possible). Patients are not required to sign the paper consent form if they have consented via the witnessed remote verbal consent process. However, the detailed process will be described in the patients' notes and a copy of the countersigned consent filed together.

Trial procedures including baseline assessments and planning CT scans will not be undertaken until witnessed remote verbal consent or written/signed informed consent has been given and appropriately recorded in the patient's medical notes. Where appropriate,

CT scans taken as part of the participant's standard of care prior to consent may be used for planning to avoid additional radiation exposure.

On the day of surgery/randomisation, participants (whether consented verbally or in person) will be asked if they are happy to continue in the study and this information will be recorded on the randomisation form and participant's medical notes.

2.5 Randomisation

Randomisation will be performed **within three hours** prior to the planned start of the procedure. This will be done after the participant has arrived in hospital and their surgical and trial consent has been reviewed with them or their carer (see section 2.4). The three-hour window will ensure that theatres have time to prepare for a robotic case without the time to make substantial changes to list order (for example, by putting robotic cases at the start or end of the day, which may introduce systematic bias).

Participants will be randomly allocated (1:1) to the two treatment groups via a central computer-based randomisation system provided by the Warwick Clinical Trials Unit (WCTU, independent of the study team).

Minimisation will be used with a random factor and 70% weighting to balance across the whole study and stratified for age (<60 compared to ≥60), hospital site, BMI>35 (at baseline), planned implant construct (hybrid Trident Exeter or uncemented Trident Accolade) and previous contralateral hip replacement.

Randomisation will be performed by the surgeon on the delegation log, using an automated telephone system which will be available 24 hours. This will be performed away from the participant to maintain blinding, and the allocation will not be communicated to the participant, with care taken not to write the allocation on theatre documentation that might inadvertently be seen by the participant.

Participants will be randomised sequentially at site level. For example, on the day of surgery, randomisation for a second case on the same operating list should not be performed until the previous randomised participant's operation has started (as each site has only one robot, there is no risk of confusion between two theatres). Allocation concealment will be maintained by an independent randomisation team who will be responsible for the generation of the sequence. Blinding and emergency unblinding procedures are documented in section 2.7.

Stickers may be used on the participant's clinical notes to flag their inclusion in the trial (without recording allocation), depending on local site arrangements for flagging inclusion in trials.

2.5.1 Post-randomisation withdrawals and exclusions

Participants may be discontinued from the trial treatment and/or the trial at any time without prejudice. Unless a randomised participant explicitly withdraws their consent, they will be followed-up wherever possible and data collected as per this protocol until the end of the trial. Should a participant withdraw from the trial after randomisation, they will continue to be treated according to normal clinical practice. A withdrawal CRF will be completed to record their decision. Data collected up to the point of withdrawal will be retained.

Participants who are registered and have consented to join the trial, but have not yet been randomised, may withdraw at any time without prejudice. In this situation, they will not be

considered to have entered the trial and will continue to be treated according to normal clinical practice. Data collected up to the point of withdrawal will be retained as this is part of the study data for analysis, but they will not be followed-up beyond their withdrawal. Participants may be withdrawn from the trial at the discretion of the Chief Investigator and/or Trial Steering Committee (TSC) or Data Monitoring Committee (DMC) due to safety concerns. A decision to change the intervention from conventional to robotic assisted or vice versa, safety reasons after randomisation is not a reason for withdrawal, participants would be kept in the study and their data included on an intention to treat principle.
Some participants who are registered and have consented to take part in the trial may have an improvement in their symptoms and may not undergo surgery at the planned time. In this case, they will be booked for a review appointment at a later date as per standard NHS care. In these cases, participants will be given the option to remain in the trial until it has been decided that they no longer want or require surgery. If the participant no longer wants or requires THR surgery, they will be withdrawn from the trial. If participants require the operation after a period of review, the treating clinician should review the pre-operative imaging and surgical planning to see if it needs to be repeated prior to surgery. Participants should be reviewed again by a clinician capable of assessing eligibility and baseline data must be re-collected if it is **more than six months old**.

2.6 Trial treatments

Preoperative imaging and surgical planning (all participants)
Participants in both groups will have a CT scan and up to three x-rays of the lower back and pelvis before surgery. Imaging will be undertaken according to the needs of the MAKO system (an imaging manual will be prepared, the CT also includes some imaging at hip and ankle) and a three-dimensional plan will be made for the surgeon for every participant. This will be done prior to surgery, but **no more than three months** before the planned date of surgery to minimise change due to disease progression.
In order to produce the plan, the CT and x-ray images will be sent to Stryker, USA. These images will contain at least two identifiers (for example, name, hospital number or date of birth), but these will only be seen by employees of Stryker and will not be shared with any other party.
If, for unexpected reasons, the surgery is delayed such that the CT scan was performed more than three months before the actual date of surgery, then the surgeon will make a clinical decision whether to accept the use of the completed CT or repeat the scan, according to their normal clinical practice. This will be recorded but will not constitute a protocol deviation and the participant can remain in the study.
The plan provided by Stryker will describe the optimal implant size and position for restoration of leg length, offset, hip centre of rotation and stability. This will be provided for all participants, regardless of treatment allocation. During the operation, the surgeon may make adjustments to this according to their normal practice in either study arm.

2.6.1 Intervention – Robotic assisted THR surgery

A full description of the intervention and control surgical procedure will be provided in an accompanying RACER-Hip surgical manual.
The intervention treatment will be THR surgery using the MAKO robotic arm assisted system and Stryker implant constructs: Hybrid construct (Exeter cemented stem & Trident uncemented socket) or uncemented construct (Accolade uncemented stem & Trident uncemented socket). These are the only implant constructs compatible with the MAKO

robot and are very commonly used in the NHS.(7) Standardised rehabilitation and perioperative care will be used in both treatment arms.
The length of the learning curve of the MAKO system is short as there are a number of similarities to the surgical technique for conventional hip replacement surgery. The primary differences are that the robot constrains the surgeons movements to only allow the preparation of the bone and insertion of the components to be performed in the pre-planned location.

Surgical expertise

It is a prerequisite that all primary (i.e., the most senior scrubbed) surgeons in the RCT have been trained to use the MAKO system and have performed a sufficient number of robotic assisted THR procedures outside of the trial that they are familiar with the technique. Primary surgeons will only be eligible to perform RACER trial cases when they have completed the MAKO hip training course (Stryker will provide evidence to the study team), have performed MAKO hip cases outside of the trial and they and the local PI are confident that they are familiar with the technique. All primary surgeons in the trial will be required to perform both intervention and control procedures.
The primary (i.e., the most senior scrubbed) surgeon will be an orthopaedic surgeon with a Certificate of Completion of Training or on the GMC specialist register for both arms of the trial. The name of the primary surgeon will be recorded on the online portal at randomisation as their individual pin code will be used to perform the randomisation. If the primary surgeon plans to supervise another surgeon during any of the procedure this must be declared on the randomisation form before the allocation is obtained, to prevent bias due to surgeon seniority. Cases must only be done with a primary surgeon present who meets the requirements of the study to perform both intervention and control procedures. The surgery form will record whether a supervised surgeon performed any aspect of the surgery.
All other care, including the choice of anaesthetic and post-operative analgesia, will be according to usual care, the rehabilitation programme will be standardised but it is expected that this will be consistent with usual practice across the sites (see section 2.6.3).

2.6.2 Control – Conventional THR surgery

Control THR will be delivered using conventional instruments using the same Stryker implants as the intervention arm. The details of this procedure will also be documented in the RACER surgical manual, as described above. The intended implant construct will be confirmed prior to randomisation to ensure the same implants are used in both intervention and control groups. Three small sham incisions over the iliac crest will be made intraoperatively to ensure blinding.

Where changes occur from the pre-defined plan, the reasons for making these decisions will be recorded on the surgical CRF. We will also confirm the number of incisions that the surgeon will make for marker placement before randomisation.

As the surgical planning, implant type and operating surgeon will all be identical between arms, the only difference between the groups will be the delivery of the surgery itself, either with the robotic-arm system or conventional instruments.

2.6.3 Unforeseen events between randomisation and surgery

Due to necessary delay between randomisation and the beginning of the planned procedure (3 hours), there is a small possibility that a participant may become ineligible in

this window. For example, a suspected myocardial infarction on the way to surgery. In cases where this happens and the participant is well enough to undergo surgery within 72 hours of the randomisation date, the participant will receive their planned allocated treatment.

In cases where this happens and the patient cannot receive their allocated treatment within 72 hours, the study team will arrange for the deletion of the original randomisation. If the patient wishes to participate at a later date, they will then be subsequently randomised again and receive a new treatment allocation. These cases will be considered 'became ineligible between randomisation and intervention' and this will be reported as such on the CONSORT chart. The original allocation will no longer be valid and will not count towards recruitment totals.

2.6.4 Rehabilitation programme post-surgery

We will recommend a standardised physiotherapy programme for all participants across both arms of the study. The provision of a self-directed physiotherapy programme is in accordance with the NICE (NG157) recommendations.(29)This is outlined below:

- Exercise prescription and gait re-education to begin on the day of, or day following THR surgery.
- Prior to discharge, all participants will be provided with a standardised, RACER-Hip rehabilitation booklet. This will provide advice about recovering from the THR, returning to activities and an exercise programme. The booklet and manual will be available on a public website. Using this booklet, prior to discharge, a member of the ward physiotherapy team will prescribe each patient exercises from a core list of eight exercises (lower limb range of motion, strength and balance). Using this, patients will be instructed to exercise at a Borg Scale of Perceived Exertion of Moderate activities, register 11 to 14 on the Borg scale ('fairly light' to 'somewhat hard'), progressing to 'strenuous activities' registered 15 or higher ('hard' to 'very, very hard') depending on their capabilities.
- A member of the hospital physiotherapy team will assess whether a patient requires supervised out-patient physiotherapy after discharge. Additional support may be required due to muscle weakness, difficulties in mobilising or functional tasks, or suspected difficulties in being unable to adhere to a self-directed physiotherapy programme. Similarly, the referring physiotherapy team member may decide that a patient cannot manage self-directed physiotherapy programme due to motivational reasons, thereby justifying a home-based assessment or out-patient referral. This reflects the recommendations made by the NICE NG157 clinical guidance.(29) The out-patient physiotherapy programme offered in such out-patient settings will mirror that of the self-directed rehabilitation booklet, the exception being that this will be supervised by a member of the physiotherapy team, rather than self-directed by the patient at home. The out-patient physiotherapy version of this will be summaries and documented in a physiotherapy manual. We will record how frequently out-patient physiotherapy referral is required for participants in the experimental and control groups.

The rehabilitation booklet and out-patient physiotherapy manual will be prepared by the research team. The programme will be reviewed by participating physiotherapy teams across trial sites. This will ensure the programme can be delivered in all participating sites. The programme will be consistent with current standard of care across the NHS, whilst meeting NICE recommendations.(29) This review by physiotherapy teams from participating sites will be performed remotely via email and (if required) video conferencing meetings. If discrepancies between the sites occur, an online consensus meeting will be arranged to ensure that agreement is reached on the components of the physiotherapy programme and associated paperwork. The physiotherapy components will be reported in line with TIDieR and CERT criteria.(30, 31)

2.7 Blinding

2.7.1 Methods for ensuring blinding

Participant and assessor blinding will be strictly maintained throughout the study, until after the two-year follow-up is reported. Assessors will be considered anyone who may assist participants in completing outcomes, such as nursing or research staff recording post-operative pain scores or at any time point.

Theatre staff will be instructed not to divulge the allocation, either verbally or by writing the allocation on widely available theatre lists. If regional anaesthesia is used intra-operatively, drapes and headphones with music will be used to maintain blinding. Regional anaesthesia is widely used, along with drapes and headphones, to preserve sterility and reduce anxiety during the operation. It is recommended that robotic equipment is kept in theatre for all THR procedures.

Additional incisions will be used in the control group to ensure blinding as documented above, these incisions are approximately 5mm in length.

The operation note will be blinded using methods from START:REACTS (NIHR EME 16/61/18), as our practical experience of acting as a recruitment site on other blinded studies is that the operation note presents a potential weak point in maintaining blinding. A standardised written template for the operation note will be prepared for sites (allowing details to be added, such as approach, implant sizes and ligament releases) but without details of the robot. Details of the use of the robot will be recorded by the surgeon in a simple online form at the end of the operation using a custom-made, password protected online database.

Implant stickers for MAKO consumables, where they are required to be in the notes, will be placed on a sheet inside an opaque envelope and placed in the medical notes. This will not unblind staff.

In clinics, the appearance of the routine post-operative radiographs will be concealed from the participants (there may be small holes visible for marker placements from those having robotic assisted THR, which could unblind someone aware of their significance, although these can be hard to detect). Clinical staff at all sites will be trained in the importance in maintaining blinding throughout.

Specifically, we will ask clinical teams and research staff not to comment on the presence or absence of visible marker holes on radiographs.

To test the quality of blinding, we will ask participants which arm they think they were in, after collection of the primary outcome.

2.7.2 Methods for unblinding the trial

The treatment code must not be broken except in medical emergencies when the appropriate management of the participant necessitates knowledge of the treatment randomisation. We do not expect there to be any medical emergency related to the intervention or control which might necessitate unblinding an individual trial participant, and so a formal unblinding process will not be developed for this trial.

The investigator(s) must document and report to the Chief Investigator any breaking of the treatment code.

Treatment codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual participant have been made and documented.

Our PPI group and patient co-applicants felt that patients in the study would prefer to know which treatment they received. Based on this feedback, we will inform participants of their allocation after we have completed the two year follow-up.

2.8 End of trial

The trial will end when the last follow-up has been received and no further follow-ups activities are planned.

The trial will be stopped prematurely if:

- Mandated by the Ethics Committee
- Mandated by the Medicines and Healthcare products Regulatory Agency (MHRA)
- Following recommendations from the Data Monitoring Committee (DMC)
- Funding for the trial ceases

The Research Ethics Committee will be notified in writing **within 90 days** when the trial has been concluded or within 15 days if terminated early.

3. OUTCOMES AND ASSESSMENTS

3.1 Outcome measures

We have selected outcomes in alignment with the Outcome Measures in Rheumatology (OMERACT) core dataset (32) and in collaboration with our PPI groups. Further details on the collection of the measures below are given in section 5.1 'Data collection and management'.

3.1.1 Primary outcome measure

The primary clinical-effectiveness outcome will be the between-group difference in overall hip pain and function using the 12-item Forgotten Joint Score Hip-12 (FJS-12), a patient-reported composite outcome measure capturing pain and function at 12 months. This scale was developed for hip replacement studies and has good evidence of validity, internal consistency and sensitivity to change.(32) The FJS-12 is transformed to a scale ranging from 0 to 100, where a high value indicates that the patient tends to be less aware of the affected joint when performing daily activities. We have chosen 12 months as this is the time recovery has plateaued to a level typically maintained over the medium to long term.(33)

3.1.2 Secondary outcome measures

Peri/acute post-operative outcomes (from surgery to day 3 postoperatively)

i. Duration of surgery (Time from skin incision to application of final dressing)
ii. Mean pain intensity, measured using an 11-point numerical rating scale (NRS) for 'pain right now' and 'average pain since yesterday' on the morning of each of the first three days after surgery.(34)
iii. Estimated blood loss calculated using Brecher's formula, based on pre- and post-operative Haematocrit measurements from routinely taken clinical blood measurements, and volume, if any, of blood transfused.(35)
iv. Total opioid use from the start of surgery to the end of day three. Total morphine equivalent, using conversion methods established in I-WOTCH, NIHR HTA 14/224/04)
v. Hours from surgery to hospital discharge.

The following outcome measures will be collected at baseline, three and six months, and one and two years, five and 10 years

vi. Overall hip pain and function measured using FJS Hip-12 (32)
vii. Overall hip pain and function measured using Oxford Hip Score. A 12-item well-validated and widely used score, scored 0-48 (48 being the best score) (36)
viii. Health utility measured using EQ-5D-5L (this will also be collected at six weeks) (37, 38)
ix. Participant satisfaction with THR, measured using a five-point Likert scale(39) (not at baseline)
x. Resource use using participant questionnaires
xi. Implant survival. Number of re-operations relating to THR (not at baseline)

Safety outcomes

xii. Serious adverse events related to the planning, operation, anaesthetic or the rehabilitation, see section 4 for definitions. Serious adverse events will also be reported separately according to the processes in section 4.

3.1.3 Process and fidelity measures

We will also collect data on the following metrics, which will be used to assess the fidelity of the interventions and ensure there are no residual learning curve effects in the trial:

xiii. Alignment measures at three months on a focused low-dose CT: Rotation of femoral (version angle) and acetabular (version and abduction angle) components, leg length, and offset compared to the pre-operative plan.

xiv. Participant self-reporting of out-patient physiotherapy visits.

3.1.4 Routinely collected data

At five and 10 years, we will also request NJR, ScAP and HES data to ensure we have accurate data on re-operations, especially revision surgery, as this can be particularly important in the health economic analysis.(42)

3.2 Schedule of delivery of intervention and data collection

Table 1 (continued next page): Trial Assessments

Visit	**0**	**1**	**2**	**3**	**-**
Visit Window (No. Weeks ± No. Days)	**Screening**	**Baseline**	**Surgery**	**Days 1-3 post-op**	**Notes review after discharge**
Check eligibility and provide PIS	✓				
Confirm Inclusion/ exclusion criteria		✓			
Consent		✓			
Baseline questionnaires and assessments		✓			
Request pre-operative imaging (planning CT and radiographs, within 3 months of planned date of surgery)		✓			
Confirm consent prior to surgery			✓		
Randomisation			✓		
Surgery (Intervention/Control)			✓		
Pain NRS (patient reported, site staff recorded)		✓		✓	

Visit	0	1	2	3	-
Visit Window (No. Weeks ± No. Days)	**Screening**	**Baseline**	**Surgery**	**Days 1-3 post-op**	**Notes review after discharge**
Opioid use, blood results, time to discharge, theatre timings				✓	✓
PROMs – FJS, OHS, (paper/electronic)		✓			
EQ5D (paper/electronic)		✓			

Table 1 (continued from previous page) Trial Assessments

Visit	4	5	6	7	8	9	10
Visit Window (No. Weeks ± No. weeks)	**6 weeks (±2 weeks)**	**3m (-2 to +6 weeks)**	**6 m (-6 weeks before due date +8 weeks after due date)**	**12 m (6 weeks before due date +8 weeks after due date)**	**24m (6 weeks before due date +8 weeks after due date)**	**5yr (6 weeks before due date +8 weeks after due date)**	**10yr (6 weeks before due date +8 weeks after due date)**
PROMs - FJS, OHS, (paper/electronic)		✓	✓	✓	✓	✓	✓
EQ5D (paper/electronic)	✓	✓	✓	✓	✓	✓	✓
Post-operative CT		✓					
OPD review & check PROMS completion				✓			
Resource use		✓	✓	✓	✓	✓	✓
Adverse Events	✓	✓	✓	✓	✓	✓	✓
End of trial							✓
Pain NRS (patient reported, site staff recorded)	✓						

3.3 Radiological assessments

The radiological studies planned for this trial will be described in a detailed radiology manual, which will be available on the trial website. Training and instruction for research sites will be available if required.

Participants in both groups will have a CT scan and up to three radiographs of their pelvis and lower back before surgery. A three-dimensional plan will be made for the surgeon, isolating the effect of the robot from surgical planning (see section 2.7.1). At three months, participants will undergo a focused, low-dose CT to measure rotation of femoral (version angle) and acetabular (version and abduction angle) components, leg length, and offset compared to the pre-operative plan. The radiological assessments do not need to be performed at the exact same time as completion of the three-month CRF, which will mostly be performed remotely by the central trial team.

Reimbursement: For this appointment, participants will be given a £20 shopping voucher to reimburse travel and parking expenses and this will be provided at 3 months post-randomisation.

We have developed a CT and X-Ray protocol to minimise the radiation dose to the smallest level required to complete the study. The total radiation dose for participants in the study (including pre- and post-operative imaging) has been calculated as 10.5mSv (pre-op 5.8mSv and post op 4.7mSv). The additional risk of cancer from a 10.5mSv scan is 0.05% over a lifetime, on a baseline risk of 50% and is equivalent to around four years and seven months of exposure to natural background radiation. This corresponds to a risk of fatal cancer induction of approximately 1 in 1,900. This has been discussed with our PPI groups who reported that they had no objections to the radiation dose and found the percentages easier to understand than the ratio.

If the participant requires any additional scans as part of the trial or the intervention (for example, a scan was inadequate and had to be repeated), these will be reported to the trial team and recorded in a study log.

We will also collect from sites the last routine care pelvis x-ray series performed, prior to entry into the trial. These will be anonymised and transferred using site specific preferred secure methods.

4. ADVERSE EVENT MANAGEMENT

4.1 Definitions

4.1.1 Adverse Events (AE)

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation participant taking part in health care research which does not necessarily have a causal relationship with the research. An adverse event can be any unfavourable and unintended sign (including an abnormal laboratory finding or ECG result), symptom, or disease that occurs during the time a participant is involved in the trial whether or not it is considered to be related to the intervention.

For the purposes of this trial, AEs should only be recorded for:

- Any adverse event that occurs during the inpatient stay (after randomisation) for the primary hip replacement
- Any hip or lower limb condition in the same limb as the trial hip.
- An adverse event related to the anaesthetic, surgery, hospital admission, physiotherapy or radiographic assessment, including any diagnosis of cancer.

- Any event where it is thought there may be a relationship to the trial interventions, trial processes or the condition being studied.

AEs will be collected from the point of randomisation onwards, up to 3 months. Events occurring before randomisation will not be recorded, with the exception of events related to the pre-operative CT (including new diagnosis of cancer) which will be recorded and reported separately.

An adverse device effect (ADE) is an adverse event related to the use of an investigational medical device. This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the installation, the operation, or any malfunction of the investigational medical device. This also includes any event that is a result of a user error or intentional misuse. These will be recorded on appropriate CRF's.

Some events which occur during treatment and recovery will be considered normal aspects of the anaesthetic and post-operative recovery process and will not need reporting unless in the opinion of the clinical team, they are untoward, excessive or outside of what might normally be expected for the procedure. These are not expected adverse events, they are normal events that occur frequently after surgery. These include:

- Nausea and/or vomiting after surgery.
- Drowsiness or headache after surgery.
- Temporary low blood pressure after surgery.
- Sore throat after surgery.
- Itching after surgery.
- Post-operative pain (note that this will be collected as an outcome) unless this is considered abnormal by the treating clinical team.
- Memory loss or confusion during the hospital stay only, or which the treating clinician believes is due to analgesics.
- Early wound oozing which spontaneously resolves.
- Swelling, within the confines of what is considered normal for total hip replacement by the treating clinical team.
- Restriction of range of motion, within the confines of what is considered normal for THR by the treating clinical team.
- Bruising, unless this is considered abnormal by the treating clinical team.
- Mild discomfort during or immediately after physiotherapy (in-patient and out-patient).

All adverse events will be monitored for trends, see section 4.3 for responsibilities.

4.1.2 Expected Adverse Events and Serious Adverse Events

Some events will be considered expected AEs (or serious adverse events, if they meet the criteria). In certain cases, the diagnoses will be confirmed, where there is uncertainty, by the treating clinician. These include, but are not limited to, the following.

Those related in general to surgery and anaesthetic:

- Injury to teeth, mouth or throat during anaesthetic
- Urinary retention
- Chest infection
- Myocardial infarction

- Stroke
- Death
- Nerve or vessel injury due to local anaesthetic (i.e. local blocks or spinal anaesthetic).
- Spinal haematoma.

Those related to the operation itself:

- Exacerbation/persistence of hip pain beyond what is considered normal by the treating clinical team. As this outcome will be captured in Patient Reported Outcome Measures (PROMs) throughout the study, only medical interventions for persistent hip pain need to be reported.
- Surgical site Infection
- Wound healing problems
- Fracture, or ligament or tendon damage or rupture
- Implant failure, dislocation or loosening
- Revision surgery or other corrective surgery
- Thrombosis (deep vein thrombosis, pulmonary embolus, cerebral infarct)
- Damage to nerves or vessels in the surgical area

Those related to physiotherapy:

- Persistent muscle soreness or muscle injury
- Bruising

Where participants are lost to follow-up, we will document SAEs identified from HES and NJR/ScAP data (see 3.1.3).

4.1.3 Device deficiency

Inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance, such as malfunction, misuse or use error and inadequate labelling.

4.1.4 Investigational medical device

Medical device being assessed for safety or performance in a clinical investigation.

4.1.5 Serious Adverse Events (SAEs)

A Serious Adverse Event is an AE that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Is an important medical condition.

4.1.6 Serious Adverse Device Effect (SADE)

Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event. This would usually not need specific unblinding (as any potential

event would likely occur at the time of surgery and therefore be identified by the unblinded surgeon) but unblinding can be performed by the unblinded members of the central trial team (the TM or trial statistician) if needed for the purposes of confidential reporting.

4.1.7 Unanticipated Serious Adverse Device Effect (USADE)

Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.
NOTE: Anticipated: an effect which by its nature, incidence, severity or outcome has been previously identified in the risk analysis report.

4.2 Reporting SAEs

All **SAEs, SADEs and USADEs** (except for the defined expected events in 4.1.2 which will be reported as outcomes) occurring from the time of randomisation until 90 days post-randomisation must be recorded on the SAE Form in the participant's CRF and emailed to an NHS email account to the Sponsor, WCTU for this purpose, **within 24 hours** of the research staff becoming aware of the event.

Events occurring before randomisation will not be recorded, with the exception of events related to the pre-operative CT which will be recorded and reported separately.

For each **SAE** the following information will be collected:

- full details in medical terms and case description
- event duration (start and end dates, if applicable)
- action taken
- outcome
- seriousness criteria
- causality (i.e. relatedness to intervention), in the opinion of the investigator
- whether the event would be considered expected or unexpected.

Any change of condition or other follow-up information should be emailed to the Sponsor as soon as it is available. Events will be followed up until the event has resolved or a final outcome has been reached. An outcome of 'unknown' is not considered to be an acceptable final outcome. An outcome of 'not yet resolved' is an acceptable final outcome for non-serious AEs at the end of a patient's participation in a trial, and for SAEs at database lock.

SAEs will be reported using the SAE form in the participant's CRF. The PI in each centre must report any SAEs to the trial coordinating centre within 24 hours of them becoming aware of the event. In the event that the PI is unable to report within 24 hours, or is unavailable, any nominated person on the delegation log may send an unsigned SAE form. Further details should then be sent by site as soon as practically possible.

AEs or SAEs may be identified by the coordinating centre from the CRFs, either from specific questions or from answers within PROMs. If this occurs, the coordinating centre may query the site for details of the event either if it is unclear, or in the case of all SAEs (for the purposes of the sites own clinical governance). This will be determined on a case-by-case basis, and the potential to do so will be included in the participant information sheet (PIS).

The SAE form should be completed and emailed to the study team: racer-hip@warwick.ac.uk and WCTU QA team: wctuqa@warwick.ac.uk. The TM will liaise with

the investigator to compile all the necessary information. The trial coordinating centre is responsible for reporting any related and unexpected SAEs (i.e. events that are serious, related and not on the list in section 4.1.2) to the sponsor and REC within required timelines. Events which are possibly, probably or definitely related to the trial intervention and are unexpected **will be reported to the REC within 15 days**.

The legal responsibility for reporting SADEs lies with the manufacturer or their authorised representative. However, the MHRA also has a voluntary reporting requirement for 'users' of devices i.e. where a device is being used in a trial in which the manufacturer has no involvement, and in this case, the coordinating centre would submit the appropriate reports and also inform the manufacturer of the event.

The causality of SAEs (i.e. relationship to trial treatment) will be assessed by the investigator(s) on the SAE form using the following descriptions:

Relationship to trial medication	Description
Unrelated	There is no evidence of any causal relationship
Unlikely to be related	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial intervention or device). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatment).
Possible relationship	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial intervention or device). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments).
Probable relationship	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Definitely related	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

All SAEs will be recorded for inclusion in annual reports to the research ethics committee.

The following process will be used to review individual SAEs

- Clinical review (by a clinical TMG member) of a line listing of all life-threatening SAEs or SAEs resulting in death within one week of their occurrence.
- Clinical review of a line listing of all other SAEs on a monthly basis at TMG meetings

The following process will be used to independently monitor trends in SAEs in addition to usual trial safety monitoring procedures.

- Cumulative review of all safety information by the DMC on a 6-monthly basis.
- All others AEs conveyed are recorded and reported annually to the DMC

A member of the Principal Investigator's trial team will be instructed to closely monitor each participant who experiences an AE until the outcome of the AE has been determined.

4.3 Responsibilities

Principal Investigator (PI):

- Checking for AEs when participants attend for treatment / follow-up.
- Using medical judgement in assigning seriousness and causality.
- Ensuring that all SAEs are recorded and reported to the Sponsor within 24 hours of becoming aware of the event and provide further follow-up information as soon as available. Ensuring that SAEs are chased with Sponsor if a record of receipt is not received within two working days of initial reporting.
- Ensuring that AEs are recorded in line with the requirements of the protocol.

Chief Investigator (CI) / delegate or independent clinical reviewer:

- Clinical oversight of the safety of patients participating in the trial, including an ongoing review of the risk/benefit.
- Using medical judgement in assigning expectedness.
- Immediate review of all related and unexpected SAEs
- Review of AEs/SAEs in accordance with the trial risk assessment and protocol as detailed in the Trial Monitoring Plan.
- Production and submission of annual reports to the relevant REC.

Sponsor (University of Warwick under co-sponsorship agreement):

- All AEs (which meet the criteria in 4.1.1) will be recorded in the CRF
- Central data collection and verification of AEs, and SAEs, according to the trial protocol.
- Reporting safety information to the CI, delegate or independent clinical reviewer for the ongoing assessment of the risk/benefit according to the Trial Monitoring Plan.
- Reporting safety information to the independent oversight committees identified for the trial (Data Monitoring Committee (DMC) and/or Trial Steering Committee (TSC)) according to the Trial Monitoring Plan.
- Expedited reporting of related and unexpected SAEs to the REC within required timelines.
- Notifying Investigators of related and unexpected SAEs that occur within the trial.
- The unblinding of a participant for the purpose of expedited reporting, only where strictly necessary.
    - Reporting of SAEs to Stryker under the timelines agreed with the company.
-

Trial Steering Committee (TSC):

- In accordance with the Trial Terms of Reference for the TSC, periodically reviewing safety data and liaising with the DMC regarding safety issues.

Data Monitoring Committee (DMC):

- In accordance with the Trial Terms of Reference for the DMC, periodically reviewing unblinded overall safety data to determine patterns and trends of events, or to identify safety issues, which would not be apparent on an individual case basis.

4.4 Notification of deaths

All deaths where there may be a relationship between the trial interventions or the condition being studied (in this case, any hip or lower limb condition, or an event related to the anaesthetic, surgery, hospital admission, physiotherapy or radiographic assessment, including any diagnosis of cancer) will be reported by the CI to the sponsor. This report will be as soon as the CI becomes aware of the event. Reporting processes to other organisations (REC and the manufacturer) will be as documented above.

4.5 Reporting urgent safety measures

If any urgent safety measures are taken the CI/Sponsor shall immediately and in any event no later than three days from the date the measures are taken, give written notice to the relevant REC of the measures taken and the circumstances giving rise to those measures.

5. DATA MANAGEMENT

Personal data collected during the trial will be handled and stored in accordance with the 2018 Data Protection Act, General Data Protection Regulation and WCTU SOPs.

Personal identifying information will be held at WCTU for follow-up purposes, paper copies will be stored separately from the trial data, in electronic databases which will be handled separately. Handling of personal data will be clearly documented in the patient information sheet and consent obtained.

Disclosure of confidential information will only be considered if there is an issue which may jeopardise the safety of the participant or another person, according to Warwick Standard Operating Procedures (SOP 15 part 1) and the UK regulatory framework. There is no reason to expect this situation to occur in this trial more than any other.

5.1 Data collection and management

5.1.1 Case Report Form (CRF) design and management

The CRFs will be developed by the TM in consultation with CI, Trial Statistician, Health Economist and other relevant members of the trial team to collect all required trial data. They will be produced in English only.

A suitably trained member of the research team (listed on the site delegation log) at sites will complete and return the CRFs to the RACER-Hip trial office. The coordinating team will check and enter the data on to a secure trial database held at WCTU as outlined in the data management plan and in accordance with Warwick SOPs.

Source documents are where data are first recorded, and from which participants' CRF data are obtained. These include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarised into the CRF), clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

CRF entries will be considered source data if the CRF is the site of the original recording (e.g. there is no other written or electronic record of data). All documents will be stored safely in confidential conditions. On all trial-specific documents, other than the signed consent, the participant will be referred to by the trial participant number/code, not by name.

5.1.2 Surgical Data and Robot session files

The data collected in the RACER-Hip study include participants' CT scans, as well as data collected by the robot during surgery. Participants will be given the option to consent for the University Hospitals Coventry and Warwickshire and the University of Warwick to share these data with the company that makes the robots (Stryker Orthopaedics), who may pay the hospital and university for providing this data under a commercial and data sharing agreement. If participants do not consent to the optional data sharing, this does not prevent them from entering the study. Stryker will strictly only use participants' data for future research and development purposes (e.g., developing new and existing instruments, knee replacement products and software), outcome studies and related publications aimed at improving patient care, this will provide commercial benefits for them.

Legal agreements are in place between Stryker, the University Hospital of Coventry and Warwickshire and the University of Warwick to protect participants' identity and personal

information will be held confidentially in accordance with GDPR. These protections will remain even if data is transferred outside the EU, such as to the USA. Stryker will hold data from previously received CT scans for the purposes of planning the surgery, and could potentially use it for linkage of with the session files and surgery data. However, will have strict contracts in place to ensure data confidentiality is maintained.

5.1.3 Data collection processes

Baseline data including PROMs will be captured on a CRF by the site research teams after consent but before surgery. Typically, this will be in the same visit as the consent visit, but it may also be collected over the phone or on paper via post when and where this method of collection is the most appropriate. The baseline assessment will be valid as long as it is taken **within six months** of the surgery. If the time between baseline data collection and surgery is more than six months, it will be repeated and the data within the four month time window will be used as the baseline.

Data related to the surgery itself will be captured on appropriate CRFs but information which could unblind someone reading the standard operation note will be recorded on the operation note CRF (mostly online but with paper backup, see section 2.7: Blinding).

For the three days post-operatively, an 11-point numerical rating scale (NRS) for 'pain right now' and 'pain since yesterday' will be collected by site staff listed on the delegation log, on the morning of each of the first three days after surgery. If the patient has been discharged, these data will be collected remotely either by paper CRF given to the participant, by telephone, or by an electronic system.

Data on opioid use, blood results, time to discharge and theatre timings will be collected by site research staff on a dedicated CRF based on review of clinical notes and/or hospital records.

Participant-reported outcomes will be collected by the central coordinating centre at three, six and 12 months and at two, five, and 10 years. At 12 months (the primary outcome), participants will undergo clinical review at the site, the cost of this has been covered within the SoECAT. At this review, the 12 month CRF may also be administered to improve data collection and follow-up rates at that key time-point.

5.1.4 Procedures for preventing missing data

Various methods will be used to reduce the rate of missing data or unreturned questionnaires including post, phone, text and email, the procedures for managing this will be outlined in the data management plan and appropriate consent will be sought to contact participants via these methods if required. To maximise follow-up, appropriately trained staff members may follow-up participants at home or alongside hospital visits to collect the primary outcome measure. Data will still be collected for participants who discontinue or deviate from the intervention protocol, unless they withdraw their consent (see section 2.4).

Multiple contact details will be recorded at baseline, with appropriate permissions, such as collection of addresses and telephone numbers, mobile telephone numbers and email addresses and contact details of next of kin to prevent loss to follow-up. Next of kin details are valuable but the participant should sign to confirm that their next of kin person is aware of this and happy for their information to be shared for this purpose. This information will

be held separately from the trial data to uphold anonymisation. If the participant is lost to follow-up at a certain time point, reasonable efforts will be used to acquire outcome data at each time point, as defined in the data management plan.

5.2 Database

The database will be developed by the Programming Team at WCTU and all specifications (i.e. database variables, validation checks, screens) will be agreed between the programmer and appropriate trial staff.

5.3 Data storage and entry

All essential documentation and trial records will be stored at Warwick Clinical Trials Unit in conformance with the applicable regulatory requirements and access to stored information (paper and electronic) will be restricted to authorised personnel. All paper data will be stored in a designated storage facility within the UHCW and/or WCTU (a restricted access building). Electronic data will be stored on password protected university computers in a restricted access building. Guidelines for data management will be outlined in the trial data management plan.

5.4 Data access and quality assurance

All data collected will be anonymised after the collection of the baseline demographic data for each participant, except where anonymisation is not possible such as contact details for follow-up, in which case it will be kept separate from the outcome data.

Confidentiality will be strictly maintained and names or addresses will not be disclosed to anyone other than the staff involved in running the trial. Participants will be identified by ID number, initials and age only where necessary. Any identifiable participant data will be held separately in a locked filing cabinet and coded with the trial number to tag identifiable data to the outcome data.

Direct access to source data/documents will be available for trial-related monitoring or audit by UHCW or WCTU for internal audit, or ethics committees.

The PI must arrange for retention of trial records on site in accordance with GCP and local Trust's policies.

5.5 Data Shared with Third Parties

De-identified data that underlie the results reported in the study will be available for non-commercial use, up to one year after publication of the final trial data, or from metadata stored in a university repository up to 10 years without investigator support. In order to access trial data, third parties must complete a data-sharing agreement with the sponsors, have an ethically approved protocol in place for use of the data, and agree the approved protocol with the RACER-Hip TMG. Data may be used for commercial purposes, according to the conditions above, but will need specific agreements in place prior to access being agreed, this may include a licence fee. Analyses may include individual patient data meta-analyses or other purposes as agreed with the RACER-Hip TMG.

Available data will include (but is not exclusive to) de-identified individual participant data that underlies the results reported in trial publications, the study protocol, statistical analysis plan, master copy of the informed consent sheets and analytic codes used.

After a year following the publication of the final report, the data will be stored in a university repository, it may still be available according to the conditions laid out above but may not receive investigator support.

5.6 Archiving

Trial documentation and data will be archived for at least 10 years after completion of the trial.

6. STATISTICAL ANALYSIS

6.1 Power and sample size

The standard deviation of the Forgotten Joint Score (range 0-100) for THR in the UK is 32.(40) For this study, a between group difference of 12 points has been chosen as a worthwhile difference, equating to a 20% difference in the total score at 12 months, assuming that the control mean score is 60. This corresponds to a moderate standardised mean difference of 0.375, which is appropriate for a highly expensive and disruptive intervention such as this.(32) With alpha 5% and power 90%, data are needed from 302 participants. With 20% loss to follow-up the sample size is **378 participants**. As this is an equipoise study, with all surgeons able to perform both procedures, we have not accounted for surgeon clustering.

Table 1: Sample size options

Mean difference	SD	Effect size	Total number needed	Total number with 20% loss to follow up
11	32	0.34	358	448
12	32	0.375	302	378
13	32	0.41	258	322

6.2 Statistical analysis of efficacy and harms

6.2.1 Planned recruitment rate

We estimate recruitment of five particpants/centre/month. In previous joint replacement trials we have recruited at 5-12/centre/month (EXACT, PAKA, SAFE-TKR). At least 500 THRs per year were performed at each of the seven proposed sites in 2019. With a staggered start of sites, we anticipate recruitment will take 16 months across five sites.

6.2.2 Internal pilot and stop-go criteria

The first eight months of recruitment will act as an internal pilot, which will be assessed at the end of month eight of recruitment. Recruitment (defined as number consented) and randomisation targets will both be set as five per centre, per month. We have allowed four months delay for waiting lists between consent and randomisation. Our projection (100%) is to achieve 180 consented participants and 80 randomised participants by the end of month eight of recruitment.

For recruitment, the recruitment rate at eight months will be calculated as the total number of people providing consent (i.e. registered) divided by the number of whole months that each site has been open to recruitment. For randomisations, the same approach will be used, but will assume no activity in the first four months once each site opens (i.e. waiting list delay). If there is conflict between the two targets, the randomisation target will be used as the primary determinant of feasibility. We will apply traffic-light stop-go rules as used previously in KARDS, ARTISAN, and START:REACTS (NIHR HTA 13/84/10 & 16/167/56, NIHR EME 16/61/18). If recruitment (consented) is at or above 100% (n≥180 green) we will continue. If recruitment/randomisation is between 66% and 100% (n179 to 118 amber) we will inform the TSC, review processes, look to open additional sites and will undertake a further review in six months. If the amber targets have not been achieved (red), without imminent evidence of improvement (such as a large increase in consents, but waiting list delays) we will discuss stopping the trial with the TSC.

6.2.3 Statistical analysis plan

A full and detailed Statistical Analysis Plan (SAP) will be agreed with the Data Monitoring Committee (DMC) prior to any analysis taking place. Data will be analysed and reported according to the CONSORT statement.(41) Treatment effects will be presented with appropriate 95% confidence intervals. Tests will be two-sided and considered to provide evidence for a significant difference if p-values are less than 0.05 (5% significance level). All analyses will be conducted as intention to treat unless otherwise specified.
Analyses will predominately carried out using R (www.r-project.org).

6.2.4 Summary of baseline data and flow of patients

Descriptive statistics for baseline details of randomised participants will be generated, as well as for all collected outcomes at each time point.

Baseline data will be summarised to check comparability between treatment arms, and to highlight any characteristic differences between those individuals in the study, those ineligible, and those eligible but withholding consent.

A CONSORT flow diagram will be produced and will be updated for TMGs, TSCs and DMCs at the study progresses (http://www.consort-statement.org)q.

6.2.5 Primary outcome analysis

The primary analysis will be on an intention-to-treat basis, modelling the FJS using a generalised linear model including baseline FJS, allocation group, age, gender, BMI (>35), implant construct (hybrid or uncemented) and previous contralateral hip replacement.

6.2.6 Secondary outcome analysis

Secondary outcomes will be analysed using an approach appropriate to data type and distribution. The main secondary outcome for early postoperative pain will be the mean NRS for pain ‘right now’ across the first three post-operative days (morning day one to morning day three). Process and fidelity measures will be reported, using an approach appropriate to data type and distribution.

Exploratory analysis will be performed of the differences between the final planned alignment and the achieved alignment measured with the radiographic measures (for all cases) as well as the final alignment recorded by the robotic system (for robotic cases only). We will examine the surgical process and fidelity measures with respect to the experience of the individual surgeon to determine whether there were any learning effects within the

study. If learning curves are identified in the process measures, their potential effect on the FJS at 12 months will also be explored.

Missing data will be scrutinized and where possible, the reason for missingness recorded. If appropriate, multiple imputation will be used with imputed data sets reported as secondary analyses alongside an appropriate set of sensitivity analyses, dependent on missingness type.

6.3 Subgroup analyses

A pre-specified sub-group analysis will be undertaken to explore whether the intervention effect differs between:

- BMI (>35)
- implant construct (hybrid or uncemented)

The subgroup analyses will follow the methods described for the primary analysis, with additional interaction terms incorporated into the mixed-effects regression model to assess the level of support for these hypotheses.

The study is not powered to formally test these hypotheses, so they will be reported as exploratory analyses only, and as subsidiary to the analysis reporting the main effects of the intervention in the full study population.

6.4 Subject population

The primary analysis and any applicable secondary analyses will be applied to an all-randomised population on an intention-to-treat basis, that is any subject randomised into the study, regardless of whether they received study intervention and regardless of protocol deviations, unless specified elsewhere in this protocol.

6.5 Health Economic Evaluation

A prospectively planned economic evaluation will be conducted from a NHS and personal social services perspective, according to the recommendations of the NICE reference case.(42) Participants' health service contacts, made in connection with their hip replacement, will be recorded at three, six and 12 months. Time lost from work (paid/unpaid) will also be recorded. Participants will be encouraged to use an electronic or paper calendar to help recall this information at follow-up. Differences in index surgical procedures with be explored through micro-costing use of surgical time and facilities. Healthcare resource use will be costed using most recently available published national reference costs, reflated to a common year.(43, 44)

Generic health-related quality-of-life will be assessed at baseline, six weeks, three, six and 12 months using the EQ-5D-5L questionnaire, and also at two, five and 10 years. EQ-5D-5L scores will be converted to health status scores using the UK value set recommended by NICE guidance at the time of analysis.(45) Using the trapezoidal rule, the area under the curve of health status scores will be calculated, providing patient-level QALY estimates. Mechanisms of missingness of data will be explored and multiple imputation methods will be applied to impute missing data. Imputation sets will be used in bivariate analysis of costs and QALYs to generate incremental cost per QALY estimates and confidence intervals.(46-49) Findings will be analysed and visualised in the cost-effectiveness plane, as cost-effectiveness acceptability curves, net monetary benefit and value of information analysis. A within-trial analysis will use the first 12 months of data, to correspond to the primary analysis. If incremental costs and benefits are nonconvergent within the trial follow-up then

extrapolated modelling will be considered, drawing upon longer term EQ-5D-5L responses, as well as failure rates and sequelae sourced from NJR and/or HES.

A limitation of trial-based economic analyses of emergent technologies is that they may not accurately represent real costs of use, or the potential broader economic impact on the NHS. Use of the robot is through a monthly hire cost, with cost per procedure dependent on hospital throughput. Sensitivity analysis will be performed reflecting current NHS throughput for THR using NJR data. Modelling may also allow the potential long-term risks of radiation dose from the CT to be explored. The costs of technologies can change in response to market conditions. The impact of technology cost will also be explored through sensitivity analysis, including a threshold analysis of varying technology cost and throughput, to guide future NICE technology appraisal and NHS policy decisions.

7. TRIAL ORGANISATION AND OVERSIGHT

7.1 Sponsor and governance arrangements

University Hospitals Coventry and Warwickshire and University of Warwick co-sponsor the trial, although the lead contracting organisation is UHCW. The day-to-day running of the trial, oversight and monitoring will be coordinated by WTCU and managed according to Warwick SOPs. UHCW SOPs will be used for contracting.

7.2 Ethical approval

All ethical approvals for the trial will be sought using the Integrated Research Application System. The trial will be conducted in accordance with all relevant regulations and guidelines.

Before enrolling patients into the trial, each trial site must ensure that the local conduct of the trial has the agreement of the relevant NHS Trust Research & Development (R&D) department. Sites will not be permitted to enrol patients into the trial until written confirmation of R&D capacity and capability is received by the co-ordinating team.

Substantial protocol amendments (e.g. changes to eligibility criteria, outcomes, analyses) will be communicated by the trial team to relevant parties i.e. investigators, RECs, participants, NHS Trusts, trial registries, journals, as appropriate.

Annual reports will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended. The REC and sponsors will be notified of the end of the trial (whether the study ends at the planned time or prematurely).

The CI will submit a final report to the required authorities with the results, including any publications within one year of the end of the trial.

7.3 Trial Registration

The trial will be registered with the International Standard Randomised Controlled Trial Number (ISRCTN) Register. A protocol paper will be published prior to completing recruitment.

7.4 Notification of serious breaches to GCP and/or trial protocol

A “serious breach” is a breach which is likely to effect to a significant degree –

(a) the safety or physical or mental integrity of the subjects of the trial; or

(b) the scientific value of the trial

If a serious breach occurs:

- the sponsor will be notified immediately of any case where the above definition applies during the trial conduct phase
- the sponsor of a clinical trial will notify the licensing authority in writing of any serious breach of
  (a) the conditions and principles of GCP in connection with that trial; or
  (b) the protocol relating to that trial, as amended from time to time, within 7 days of becoming aware of that breach

7.5 Indemnity

NHS indemnity covers NHS staff, medical academic staff with honorary contracts, and those conducting the trial. NHS bodies carry this risk themselves or spread it through the Clinical Negligence Scheme for Trusts, which provides unlimited cover for this risk. The University of Warwick provides indemnity for any harm caused to participants by the design of the research protocol.

7.6 Trial timetable and milestones

A three-month period is planned to prepare the Health Research Authority (HRA) application. This will be performed prior to the study to ensure the trial is set-up efficiently at minimal cost. After this, the study will take 42 months (excluding longer-term follow-up) starting May 2021, the planned timetable is shown below:

Month	Date	Activity	Milestones
Phase One: Set up and Internal Pilot			
-3m to 0m	May 2021 - Oct 2021	Finalise protocol HRA/REC submission	HRA / REC approval
0m to 3m	Oct 2021 –Dec 2021	CRF design, contracts and site setup	First TSC/DMC Final version of all materials approved Two sites open
4m-12m	Jan 2022 – Oct 2022	Start recruitment to pilot (staggered start two sites beginning in first month then one per month)	Five sites open and recruiting to target 180 participants recruited for internal pilot
12m	Oct 2022	Assess against stop-go criteria (after 8 months recruitment)	Report to DMC, TSC and HTA
Phase Two: Main Study			
4m to 20m	Jan 2022 – Jun 2023	Complete trial recruitment	378 participants recruited
4m to 24m	Jan 2022 – Oct 2023	Randomisation & Surgery	378 participants randomised and surgery performed
36m	Oct 2024	Complete 12m follow up	All 12 month follow up closed
36m to 42m	Oct 2024 - Mar 2025	Data cleaning (2m), complete analysis	Present results to DMC & TSC

		(2m), final report (2m)	Final monograph and dissemination of results
Phase Three: Long term Follow up			
Out of main study period	Apr 2025 – Sep 2033	Complete 2, 5 and 10 year follow up and analysis (3 months)	Reporting of 2, 5 and 10 year follow up results

7.7 Administration

The trial coordination will be based primarily at UHCW in the WCTU, Clinical Sciences Research Laboratories, but staff will, on occasion, work at WCTU, University of Warwick.

7.8 Trial Management Group (TMG)

The TMG, consisting of the project staff, co-investigators and PPI co-investigators involved in the day-to-day running of the trial, will meet every four weeks throughout the study period, continuing at lower frequency in the follow-up period (i.e. after 42 months). Facilities will be available for in-person or teleconference as required. Major milestone TMGs will be identified and all co-investigators will be invited for face-to-face meetings at those time points. Meetings will alternate between CSRL and Birmingham to reflect the co-chief investigator arrangement in this study.

Smaller team meetings consisting of the CI, Co-CI, TM, TC, SPM and any other invited member will meet between these times when required. Significant issues arising from management meetings will be referred to the Trial Steering Committee or Investigators, as appropriate.

7.9 Trial Steering Committee (TSC)

The trial will be guided by a group of respected and experienced personnel and trialists as well as at least two 'lay' representatives. The TSC will have an independent Chairperson. Face to face meetings will be held at regular intervals determined by need but not less than once a year. Routine business is conducted by email, post or teleconferencing.

The Steering Committee, in the development of this protocol and throughout the trial will take responsibility for:

- Major decisions such as a need to change the protocol for any reason
- Monitoring and supervising the progress of the trial
- Reviewing relevant information from other sources
- Considering recommendations from the DMC
- Informing and advising on all aspects of the trial

The membership of the TSC is shown at the start of this protocol.

The full remit and responsibilities of the TSC will be documented in the Committee Charter which will be signed by all members.

7.10 Data Monitoring Committee (DMC)

The DMC will consist of The DMC will consist of a minimum of two appropriate clinicians and one statistician. The DMC will meet approximately every six months for the duration of the study.

The DMC will meet in a joint TSC and DMC meeting (unless quorate numbers for each can not be achieved, in which case they will be separated) and regularly thereafter. Confidential reports containing recruitment, protocol compliance, safety data and interim assessments of outcomes will be reviewed by the DMC. The DMC will advise the TSC as to whether there is evidence or reason why the trial should be amended or terminated.

The membership of the DMC is shown at the start of this protocol.
DMC meetings will also be attended by the CI, Co-CI, TM, TC (all at the discretion of the DMC chair and only for non-confidential parts of the meeting) and the trial statistician.
The full remit and responsibilities of the DMC will be documented in the Committee Charter which will be signed by all members.

7.11 Essential Documentation

An electronic Trial Master File will be set up according to Warwick SOPs and held securely. The coordinating centre will provide electronic Investigator Site Files to all recruiting centres involved in the trial.

7.12 Financial Support

The trial has been funded by a grant from the National Institute for Health Research, Health Technology Assessment programme. Stryker have agreed to fund surgeon training and excess treatment costs which will include additional consumables needed for robotic cases, ten minutes of theatre time for robotic cases and pre-operation CT costs for all participants, so there is no additional cost for sites that participate beyond the cost of the robot hire/purchase itself. Contractual arrangements will be in place to ensure company will not have any involvement in the design, delivery or interpretation of the study in line with NIHR policy.

8. MONITORING, AUDIT AND INSPECTION

The study will be monitored by the Research and Development Department at UHCW as representatives of the lead Sponsor and by the Quality Assurance team at WCTU as representatives of the co-sponsor, to ensure that the study is being conducted as per protocol, adhering to Research Governance and GCP. The approach to, and extent of, monitoring will be specified in a trial monitoring plan determined by the risk assessment undertaken prior to the start of the study.

A trial monitoring plan will be developed and agreed by the TMG and TSC based on the trial risk assessment. Processes to be considered in the monitoring plan will include participant enrolment, consent, eligibility, and allocation to trial groups; adherence to trial interventions and policies to protect participants, including reporting of harm and completeness, accuracy, and timeliness of data collection. This plan will be available from the trial coordination centre and will also be lodged with the sponsors. Assessment of fidelity of the interventions will be assessed using the process and fidelity measures documented in section 3.1.3.

Whilst the monitors work in the same institution as the CI and trial team (WCTU), they will act independently of the trial team in this role. Sites persistently late in reporting SAEs, receipt of multiple late/poorly completed CRFs, or evidence from CRFs that the trial protocols and procedures are not being adhered to (as assessed by the CI, Co-CI or the TMG) may be considered triggers for on-site monitoring visits. The co-sponsors will ensure investigator(s) and/or institutions will permit trial-related monitoring, audits and REC review, providing direct access to source data/documents as required. Monitoring will be performed by exploring the trial dataset or performing site visits, as defined in the trial monitoring plan.

Recruitment sites are obliged to assist the sponsor in monitoring the study. These may include hosting site visits, providing information for remote monitoring, or putting procedures in place to monitor the study internally.

9. PATIENT AND PUBLIC INVOLVEMENT (PPI)

Initial patient interviews and the formation of a patient advisory group (10 participants) has helped to develop this application. The advisory group were concerned by the growth of expensive robotic assisted hip replacement surgery within the NHS without high quality research data but were equally excited by the opportunities and potential benefits that robotic assisted hip replacement may offer. Some participants emphasised recent events reported in the media about robotic assisted surgery in the UK that had gone badly wrong and they felt robust studies like ours would help to reassure the public and patients. All the PPI stakeholders consulted with felt the research proposed was very important.

Subsequently the advisory group has helped us to build a hierarchy of outcome measures and agree methods for following up participants. The group were asked for feedback on some of the specific challenges of the study including additional scans and trial blinding. The group has highlighted way in which both could be overcome and made more acceptable, including allowing participants to know their allocation at two years and keeping the robot in theatre for all cases to help maintain blinding.

The patient advisory group have agreed to provide ongoing remote electronic and telephone support throughout the lifecycle of this trial as patient centred questions arise that our PPI co-applicants would like further advice on. This will include final approval of the patient facing material and major changes to the protocol. Many of our members are already enthusiastic about ensuring that the trial material appeals to potential participants and that medical jargon is minimised within the trial.

Two PPI representatives (Mrs Smith and Mrs Warwick) are co-applicants, both have had hip replacement surgery previously and will in the early stages of the trial help to develop all the patient facing materials and the trial processes (e.g. recruitment process). The co-applicants will also be part of regular trial management meetings. They will make a major contribution to ensuring the study findings are widely publicised in a user-friendly format for the benefit of the public and future patients. At least one further patient will be a member of the steering committee. All lay representatives will be supported by a dedicated PPI lead (Sophie Rees) and training and advice through the Warwick CTU.

At the end of the study the results will be shared at a stakeholder meeting to which we will invite members of the patient advisory group and our PPI co-applicants with the aim of developing a participant interpretation of the study findings before widespread dissemination. Our PPI members will help to write a summary of the findings which will be published on patient websites we will engage with the media through press releases to ensure the results are disseminated to as many patients as possible.

10. DISSEMINATION AND PUBLICATION

The results of the trial will be reported first to trial collaborators. The main report will be drafted by the trial co-ordinating team, and the final version will be agreed by the TSC before submission for publication (and NIHR prior to publication), on behalf of the collaboration.

The trial management team and other collaborators will prepare the study monograph within the agreed timetable, which will start to be prepared at the end of recruitment, ensuring that the results of the analysis can be inserted into a well prepared document and reducing the time to prepare the final report after the analysis.

The success of the trial depends on the collaboration of doctors, nurses and researchers from across the UK. Equal credit will be given to those who have wholeheartedly collaborated in the trial, authorship will follow ICJME guidelines (http://www.icmje.org/recommendations/) and will require sustained or substantial involvement in the trial management and/or conduct. The final decision on authorship will rest with the CI and Co-CI, who will be first and last-author, correspondingly, on the final paper.

The trial will be reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines (www.consort-statement.org).

10.1 Patients and public

Dissemination to patients and the public will be led in conjunction with our patient partners, who have been closely involved throughout the study development. Dissemination to trial participants will follow current HRA guidelines (https://www.hra.nhs.uk/planning-and-improving-research/best-practice/publication-and-dissemination-research-findings/).

We will use lay summaries and infographics which will be sent to trial participants, trial hospitals, and published on our trial website, or in conjunction with the main publication, if journal policies allow. We will prepare articles for patient focused websites such as patient.co.uk and utilise social media to report our findings. We will use press releases to alert the popular press in conjunction with our press officer. A trial website will be hosted by WCTU and used to promote study progress and trial publications.

10.2 Surgical & wider clinical community

We will register the trial with ISRCTN prior to starting and will publish the trial protocol during the recruitment phase.

We will prepare the study monograph within three months of study completion and will publish the trial results in a major peer-reviewed publication. Key findings will be presented at national and international conferences, such as the British Orthopaedic Association and the American Academy of Orthopaedic Surgeons.

10.3 Commissioners and policy makers

We will inform NICE and other policy makes of the results when they are published, as the results would be expected to have considerable impact nationally and internationally. This would be expected to contribute to future updates of the NICE Joint Replacement: Hip, Knee and Shoulder guidelines, and we will request NICE consider this for a Single Technology Appraisal (which have a stronger mandate then guidelines). The results would be expected to impact internationally, with funding decisions in Europe and the US

particularly strongly influenced by large NIHR HTA studies and NICE guidelines.

If the trial finds robotic surgery to be clinically and cost-effective, it will improve the care of patients undergoing joint replacement, the majority of whom do not have access to this technology. However, if it is ineffective the study will stop the widespread adoption of expensive technology which could lengthen or complicate treatment unnecessarily.

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