PROTOCOL

Robotic Arthroplasty: a Clinical and cost Effectiveness Randomised controlled trial (RACER)

ISRCTN Number:	27624068
Sponsor:	University Hospitals Coventry and Warwickshire (Lead Sponsor) & University of Warwick (Co-sponsors)
Funding Body:	NIHR Heath Technology Assessment programme
Ethics Approval Date:	East Midlands – Nottingham 2 Research Ethics Committee 29.07.2020
Version Number:	2.0
Date:	28.09.2020
Stage:	Final

This protocol has regard for current HRA guidance and content

Protocol Amendments:

Amendment No. 1	Date of Amendment	Date of Approval

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TRIAL SUMMARY

Trial Title	Robotic Arthroplasty: a Clinical and cost Effectiveness Randomised controlled trial (RACER)
Trial Design	Pragmatic, multi-centre, patient-assessor blinded randomised controlled trial with health economic evaluation
Trial Participants	People undergoing total knee replacement (TKR)
Planned sample size	332
Follow-up Duration	Primary outcome: 12 months Secondary timepoints: three months, six months, two years, five years, 10 years.
Planned Trial Period	From: 01/04/2020 To: 31/03/2024 (note long-term follow-up also planned through to October 2032)
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 TKR against TKR performed with conventional instruments on the Forgotten Joint Score, 12 months after surgery. *Cost effectiveness:* To determine the cost-effectiveness of robotic TKR in a UK NHS setting.
Secondary Objectives	To compare differences in intra-operative blood loss, pain in the first three days after surgery, time to hospital discharge and analgesic use between groups. To compare, between groups, the Forgotten Joint Score, Oxford Knee Score, Oxford Activity & Participation Questionnaire, EQ-5D-5L, pain intensity, satisfaction, adverse events and implant survival at three, six and 12 months; plus, two, five, and 10 years following surgery.
Objectives for Process & Fidelity Measures	To compare operation times and post-operative alignment of the knee 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
ADLs	Activities of Daily Living
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
EQ-5D-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
KL	Kellgren-Lawrence grade
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

OKS	Oxford Knee 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
QoL	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
TKR	Total Knee 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 Epidemiology and burden of the condition

1.1.1 What is the problem being addressed?

In an effort to improve clinical outcomes, expensive robotic assisted knee replacement systems are being introduced to the NHS, without evidence that they are clinically or cost effective. Without a high-quality randomised trial of clinical and cost effectiveness, we are unable to determine whether this is good for patients and the NHS or whether it is an unnecessary cost that should be discontinued.

In 2017, 109,000 total knee replacements (TKRs) were performed in the UK costing over £550M.(1-4) Their use continues to increase due to an ageing population and the rising prevalence of obesity.(2, 5) For most people, they reduce pain and improve function, although some limitation or discomfort remains for many people and dissatisfaction is relatively common.(6)

Around 15-20% of people are dissatisfied after a knee replacement; a meta-analysis found that 20% report pain as bad as or worse than before the operation, and many have ongoing restrictions to activities of daily living (ADLs).(7-9) Most people still report some functional limitation or pain from their replaced knee even after a year or more, when they are unlikely to experience any further clinical improvement.

The lifetime risk of revision for a person aged 50 having a knee replacement is around 35%, with a mean time to revision of 4.6 years.(10) Revision is a major procedure involving repeating the replacement surgery, commonly with inadequate recovery, and large healthcare costs of around £50M each year in the UK. Each year around 5,000 knee replacements are revised. Half of these are for pain, stiffness, instability or early wear, which may be preventable by more precise surgery.(2) Potentially modifiable factors such as complications, reoperations and the length of hospital stay contribute substantially to the overall cost of knee replacements to the health service.(11)

Two of the top ten questions in the James Lind Priority Setting Partnership for hip and knee replacement (12) were:

> *What (health service) pre-operative, intra-operative, and post-operative factors can be modified to influence outcome following hip and knee replacement?*
>
> *What are the best techniques to control longer term chronic pain and improve long term function following hip and knee replacement?*

The top priority question in the James Lind Priority Setting Partnership for revision knee replacement was:

> *What are the causes of persistent pain following a knee replacement? How can the pain be prevented or minimised?*

1.1.2 Why is the research important?

Surgeons are increasingly looking to the use of robotics to help improve results and reduce variation in outcomes after TKR.

Computer systems designed to improve surgical accuracy and reduce inconsistency have been tested over many years, using either computer systems to show the surgeon where

they are cutting, or by using pre-printed templates designed to fit around the patient's bone. However, the delivery of the plan remained under the control of the surgeon, who could still injure surrounding soft tissues in the same way they could with conventional jigs. Inaccuracy also remained a problem, with no improvement shown in clinical results.(13-15)

Robotic-arm systems resolve the problems of earlier computer devices by constraining the surgeon in such a way that they can only deliver the bone cuts according to a pre-planned three-dimensional template (figure 1). Much greater precision can be achieved than with standard instruments, especially in obese people, where conventional surgery is more challenging.(16) Subtle adjustments to the position of the implant can be planned and delivered in theatre by making small corrections to the software, which cannot be delivered consistently using conventional jigs or older computer systems, due to the risk of error.

Figure 1: The MAKO robot. The surgeon moves it into the surgical field, the robot controls the cuts

The causes of poor function, persisting pain and dissatisfaction after knee replacement are likely to be multi-factorial, but some of these factors may be improved with better surgical technique and precision.(17, 18) Poor implant position and sizing are associated with worse clinical outcomes.(19-22) Tibial component rotation is particularly hard to judge with conventional instruments but may have an important influence on long-term pain.(19, 20) People with pain associated with instability or stiffness have particularly high levels of dissatisfaction, which may be preventable with better surgical technique.(23) Accurate positioning of knee replacements is harder in obese individuals, also complications and dissatisfaction are more common in this population.(24)

Robotic-arm systems also reduce the need for soft-tissue dissection and prevent the saw blade injuring soft tissues around the bone, potentially allowing quicker and less painful recovery from surgery.(25, 26) Early post-operative pain may be a predictor of long-term pain and poor outcomes.(27-30) Also, less pain and soft tissue dissection in the early phase after surgery may allow people to engage with rehabilitation earlier in their recovery. Total

knee replacements are painful procedures with relatively long hospital stays; typically, 4-5 days. Reduced early pain may result in shorter inpatient stays and quicker early rehabilitation.(31)

1.1.3 Choice of intervention

MAKO has, up to 2019, been the only robotic-arm system available to the NHS (MAKO, Stryker, USA). Whilst other robotic-arm systems are becoming available, their development has been hampered by the fact that MAKO hold many of the key patents, such as the method of interaction with the surgeon and the attachment of a cutting instrument to a robotic arm. Other robotic TKR systems are much earlier in their development and clinical testing.(32) Consequently it will be many years until the safety profiles of other robots are such that they will be ready for phase III clinical studies.

The MAKO Corporation was purchased by Stryker in 2013, the technology has been stable over this time and is not expected to change in the near future. Its worldwide use is growing exponentially. Between 2017 and 2018 there has been over a threefold increase in MAKO cases, and over 60,000 TKRs have now been done using MAKO globally.

The MAKO robot is increasingly used in the NHS without good evidence that it is clinically or cost-effective. The time is now right to determine if the use of robotic-arm systems for TKR should be continued in the NHS.

1.2 Existing knowledge

A 2018 systematic review and meta-analysis of clinical effectiveness of robotic TKR reported on multiple small, low- or very-low quality RCTs; all were of older robotic technologies that have been superseded.(33) The meta-analysis contained major errors and inconsistencies that preclude any viable re-analysis. No benefit was identified for robotic systems in TKR, although results were influenced by a high complication rate in these early robotic systems, which has not been observed with the current generation of knee replacements using robotic systems.

In our current systematic review of robotic joint replacement systems (PROSPERO: CRD42019120455) we have not identified any RCTs of the MAKO system for TKR. We identified nine comparative studies of robotic systems, for TKR, with patient reported outcomes (N=1,036) published from 2002 to 2018. The study designs, the systems evaluated, and the outcomes assessed are too heterogeneous to allow meaningful meta-analysis. Nevertheless, these studies, nearly all of which used old and superseded robotic systems, typically report small positive effects on a range of clinical outcomes.

Only two studies reported on the MAKO robot for TKR.

A 2018 UK non-randomised comparative study found surprising early benefits from robotic-arm TKR using MAKO (N=40) compared to conventional instruments (N=40). These included reduced pain [Day 2 pain NRS mean difference (MD) 2.8, $p<0.001$, 95% CI not presented], hours to discharge [MD 28, $p<0.001$] and even objective measures such as haemoglobin [MD 7.5 g/L, $p<0.001$].(26) This was thought to be due to less local soft tissue damage when using the robot.(25) It is not yet known if these early apparent differences resulted in better longer-term outcomes. A 2017 non-randomised study in the USA compared MAKO TKR

(n=20) to conventional TKR (n=20) and found higher satisfaction and improved WOMAC scores at six months.(34)

A 2016 UK randomised trial (N=139) compared accuracy of bone cuts between partial knee replacement (this is different to total knee replacement) with the MAKO system, and conventional instruments with a different implant design.(35, 36) It is possible that the different implants confounded the clinical results. Bone cuts were more accurate with robotic surgery and there were non-significant differences, favouring robotic systems, in some clinical outcomes at one year [Forgotten Joint Score mean difference (MD) 10.4 p=0.285, American Knee Society Score MD 5, p=0.106] which had converged by two years.(35, 36) Statistically significant differences in gait analysis (N=71) were observed at one and five years.(37) The potential benefits for TKR, a larger procedure with lower levels of satisfaction, might be expected to be greater.

The same group have completed recruitment to a trial funded by the NIHR/MRC EME programme (TRUCK, N=94), comparing conventional TKR, to two partial knee replacements inserted on both the medial (inside) and lateral (outside) compartments of the knee using MAKO. The primary outcome is a biomechanical assessment using gait analysis, the results have not been reported yet. The eligibility criteria are for a much more restricted patient group then in RACER, and the intervention is a novel and controversial approach, is not used widely at present. It will be many years before long-term data are available to know if this technique is safe for use in routine practice.

There is a NICE guideline on 'Joint Replacement, Hip, Knee and Shoulder' currently in draft format (GID-NG10084, publication expected Summer 2020). The question of robotic surgery is not addressed in the guideline. Our findings will influence future updates of the guideline as robotic joint replacement is becoming more widespread both in the UK and worldwide.

A search of trial registries has identified three ongoing international trials comparing MAKO TKR to conventional TKR. One is a small, company sponsored trial (N=60) in France designed to assess differences in surgical accuracy between robotic and conventional surgery (clinicaltrials.gov NCT03566875). The other is a study funded by, and conducted in, a private hospital in the USA (N=248), with no evidence of support by an experienced clinical trials team (clinicaltrials.gov NCT03523897). We have been in contact with the USA trial team who are finding recruitment difficult as patients are now requesting MAKO rather than entering the trial.

A third study was registered in January 2020 (ISRCTN47889316) and is being carried out in Newcastle, UK. It will recruit 90 participants and is expected to finish recruiting before RACER starts recruitment. This study (acronym: ROAM) compares the MAKO robot and an orthosensor device (a device to test the tension of the ligaments, during the operation) to conventional TKR. The intervention is slightly different to the one tested in RACER, it is single site and may therefore be harder to generalise, and the sample size is smaller than we calculate is needed to answer our primary hypothesis. However, the experience of the team in completing their study will be invaluable in assisting the delivery of RACER and the ROAM and RACER trial teams will interact to ensure key learning points are shared.

They are all smaller trials than we propose, with insufficient statistical power. Two of the three studies are in very different health service environments. There is no evidence that health economic data will be collected in the first two studies. As such, they will not be able to determine whether the NHS should or should not recommend ongoing use of robotic-arm systems for TKR.

1.3 Need for a trial

Robotic knee replacement systems are being introduced into the NHS; at the time of writing (January 2020), eight trusts already have robotic surgery equipment, alongside multiple private institutions. They are expensive, costing around £1M in capital costs, or large hire costs (£10-20K/month), with additional consumables required. The need for a pre-operative CT adds further costs and radiation exposure. If robotic surgery were in general use the cost of consumables and CT scans alone could be in excess of £45M per year. If robotic surgery is beneficial, these costs might be offset by reduced inpatient stays, reduced post-discharge care, or reductions in highly expensive complications including revision surgery.

Because of inconsistent clinical outcomes with standard techniques, the increasing interest in robotic orthopaedic surgery in the UK is primarily driven by TKR, and the time is now right to determine whether robotic TKR is clinically and cost-effective, or whether its use in the NHS should be discontinued.

We propose an RCT of a robotic TKR system which is already being introduced into the NHS at high cost. If expensive robotic systems are not found to be clinically or cost-effective, then their use can be discontinued, making substantial savings. However, if they are clinically and cost-effective, robust evidence is needed now to ensure patients receive the best treatments and reduce the high rates of ongoing disability after TKR.

The expensive and disruptive intervention to be tested is the use of the robot assistance to perform surgery. Use of the robot also mandates the need to perform pre-operative planning using a CT scan. This raises the question as to whether CT planning itself could influence outcome. CT based pre-operative planning has not been studied independently, but previous technologies that use this (such as computer aided surgery) have not shown to have an influence on clinical outcomes.(38-40) Despite being available as an option for well over a decade, CT planning has not been taken into practice for conventional total knee replacement, as would be expected if it were a helpful intervention in its own right. Regardless, it is important to consider the possibility that it could influence outcomes in the study. Therefore, it is necessary to isolate the effects of the robotic intervention from the CT planning, by performing CT-based planning in both arms. This will also allow the study to be blinded, which will ensure a much more robust answer to the research question.

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, and the study would not answer the clinical question. If there is no difference observed in our study design (with planning in both arms), then it can be concluded with confidence that the robot does not improve clinical outcomes. Further studies could examine whether or not the much cheaper and simpler planning process has an independent effect on 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 knee replacement, is a study in which the planning process is isolated from the expensive and disruptive robotic intervention.

1.4 Research Question

What is the comparative clinical and cost effectiveness of performing primary TKR with, or without, assistance from a MAKO robot?

1.5 Aims and objectives

1.5.1 Aims

Our overarching aim is to determine whether robotic TKR is clinically and cost-effective when compared to TKR using conventional instruments.

1.5.2 Primary objectives

1) To compare robotic TKR against TKR performed with conventional instruments on the Forgotten Joint Score, 12 months after surgery.

2) To determine the cost-effectiveness of robotic TKR in a UK setting.

1.5.3 Secondary objectives

3) To compare differences in pain in the first three days after surgery, estimated blood loss, analgesic use, and time to discharge between groups.

4) To compare the Forgotten Joint Score, Oxford Knee Score, Oxford Activity & Participation Questionnaire, EQ-5D-5L, pain intensity, satisfaction, adverse events, re-operation, and implant survival at three, six and 12 months and 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.
Blinded surgical trials are rare, but where they can be used, they have been strongly recommended by the Royal College of Surgeons, as they provide the strongest evidence of effectiveness for an intervention.(41, 42) This includes the use of placebo or sham surgery where it can be performed safely.

In this study, participants in both arms will receive active treatment, the control arm will receive full active care to the same high standard received by all patients who undergo TKR 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 conventional jigs.

In robotic surgery cases, the surgeon has to make two additional small (1cm) incisions to place pins in the bone, so the robot knows where the bones are and if they are moving. The incisions for these pins would unblind participants in this study. Therefore, two additional small incisions (1cm each) in the control group will be used to blind participants to whether they had the additional bone markers used for the robot or not. These will be identical to

the 1cm incisions used for the robotic group and will be covered in the same small dressings. The PPI group had no objection to this, they were fully supportive of the use of blinding in the trial and the overall design of the study.

Participants in both groups will have a CT scan and a three-dimensional plan will be made for the surgeon, isolating the effect of the robot from surgical planning, which could in itself influence results. An Ionising Radiation (Medical Exposure) Regulations (IRMER) application will be made prior to ethics submission.

We have developed a CT protocol to minimise the radiation dose, whilst giving the necessary information to use the robot. The total radiation dose for participants in the study (including post-operative imaging, a very small dose of 0.9mSv) has been calculated as 6.1mSv. A total trial dose of 6.1mSv corresponds to a risk of fatal cancer induction of approximately 1 in 3,200 or an increased cancer induction risk of 0.03% and is equivalent to around two years and eight months of exposure to natural background radiation.
This has been discussed with our PPI representatives who reported that they had no objections to the radiation dose and found the percentages easier to understand than the ratio.

1.7 CONSORT

The trial will be reported in line with the CONSORT (*Con*solidated *S*tandards *o*f *R*eporting *T*rials) statement. (43)

1.8 Assessment and management of risk

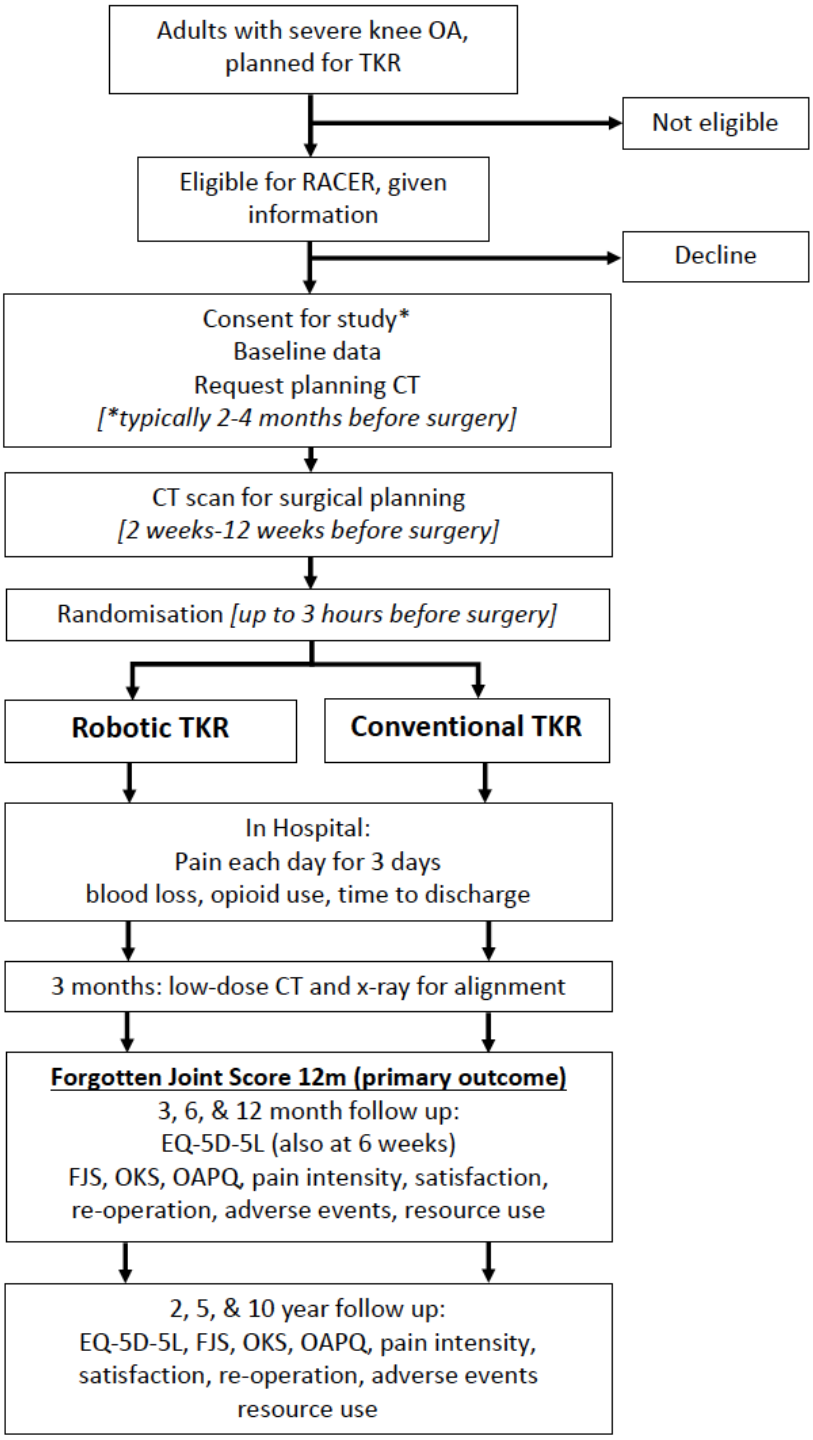
The interventions are both standard interventions, used in the NHS at present, and within their licenced indications. There is a very small additional risk related to the radiation dose (noted above). A risk assessment will be performed according to Warwick Standard Operating Procedures (SOP).

2. TRIAL DESIGN

2.1 Trial summary and flow diagram

RACER is a multi-centre, patient-assessor blinded, pragmatic randomised controlled trial to assess the clinical and cost-effectiveness of robotic TKR compared to conventional TKR in the UK NHS health setting. This is the equivalent of a phase III study according the IDEAL classification.(44)

Figure 1 Trial flow diagram



2.2 Eligibility criteria

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

2.2.1 Inclusion criteria

1. **Osteoarthritis of the knee** with pain, disability, and changes on standard of care clinical images (x-rays or MRI according to normal clinical practice) that, in the opinion of the treating clinician, **warrants TKR** (we will collect these images as a quality assurance check, see section 3.3).
2. **Conservative therapy has been unsuccessful**, as judged by the treating clinician.(45)

2.2.2 Exclusion criteria

1. **Osteoarthritis secondary to inflammatory arthropathy or intra-articular fracture**, as determined by the treating clinician
2. **Revision surgery or need for complex implants**, or any other implant than a standard Triathlon TKR, 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.
3. **Age <18 years**.
4. **Unfit for TKR**, or surgery is otherwise contra-indicated (for example, concurrent infection).
5. **Previous randomisation** in the present trial (i.e. other knee).
6. **Unable to take part in 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 knee 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 will be considered based on the processes in local sites.

The attending clinician will confirm appropriateness for study eligibility on a case report form (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), registration onto the study database 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 will be 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 at all sites and will be emailed to the co-ordinating centre monthly or completed directly on to the study database (with any identifiers redacted, except numbers for trial participants). This will include details of the number of people presenting to recruiting clinical teams who are considered suitable for knee 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

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.

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 2.6.2).

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.

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 re-operation on the affected knee, and check for adverse events with the GP as though they were 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.

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 not initialling the appropriate box on the consent form.

The investigator or their nominee and if applicable the independent witness must sign and date the consent form. One copy of this will be posted to the participant, one will be kept by the investigator/nominee, and a third will be retained in the patient's hospital record.

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 as some patients wish to consent at the time they receive the information and find additional visits a burden. Even after consent, they will have ample time to consider participation and potentially withdraw whilst waiting for surgery, which would typically be three to four months. No participant will provide initial consent for the study on the day of surgery and planning CT scans will not be 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 visit or they will be provided with a consent form to take away, sites will follow-up with a telephone call for further clarification and ask if they agree to participate. If the potential participant agrees, they will be able 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 singed consent form with them for the CT appointment (assuming appropriate procedures are in place to check this 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

A witnessed remote verbal consent process is allowed in this study 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 is not part of the study team who will declare that consent was appropriately given: 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.

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

2.5.1 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 eligibility and surgical and trial consent has been reviewed with them (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). This will be performed by minimisation with a random factor, with a 70% weighting towards balance across the whole study, stratified for age (<60 compared to ≥60), hospital site, surgeon, BMI ≥35 at baseline, and primary compartment involved (medial, lateral or patellofemoral, as determined by the treating clinician).

Randomisation will be performed by any member of the local clinical or research team on the delegation log, using an online system. A back-up automated telephone system 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 and will have no role in the allocation of participants. Blinding and emergency unblinding procedures are documented in section 2.7.

Warwick Clinical Trials Unit

Online Randomisation Weblink: https://ctu.warwick.ac.uk/racer

First back-up: Automated telephone randomisation (24 hours): +44 (0) 24 7526 2666

Second back-up: Manned telephone randomisation service (Mon-Fri 9am-5pm): +44 (0) 24 7615 0402

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.

2.5.2 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 should be completed to record their decision. Data collected up to the point of withdrawal will be retained.

Participants who are registered, but not yet 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. Routine NHS datasets related to their care (such as HES, NJR and ScAP) will still be examined for adverse events (such as re-operations) unless they also specifically withdraw from this aspect on the withdrawal CRF or consent forms.

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. Needing to change the intervention for 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 registered in the trial will have an improvement in their symptoms before receiving the intervention and may not undergo the intervention at the planned time. In this case, they will be booked for a review at a later date as it is standard in the NHS. In those 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. In case the participant no longer wants or requires surgery they will be withdrawn from the trial. In case it is decided that 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, they should be re-consented to the study and baseline data should be re-collected if its more than six months old (182 days).

2.6 Trial treatments

2.6.1 Intervention

A full summary of the intervention and control procedure will be available in an accompanying RACER surgical manual, prepared following a surgical consensus meeting to which all surgical co-investigators will be invited. This will be available on the RACER trial website.

The intervention treatment will be TKR performed using the MAKO robotic system and Triathlon (Stryker, USA) implants, the only implant compatible with the MAKO robot. All implants will be cemented (96% of TKRs recorded on the National Joint Registry (NJR) are cemented)(2). No uncemented implants will be used.

Participants in both groups will have a CT scan 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, isolating the effect of the robot from surgical planning. This is done at least two weeks prior to surgery, but no more than twelve weeks before the planned date of surgery to ensure bone shape does not change due to disease progression.

In order to produce the plan, the 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 12 weeks before the actual date of surgery, then the surgeon will make a clinical decision whether to accept the use of the current 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 will aim for neutral alignment (i.e. the leg is straight at the end of the procedure) for both arms of the study, as is normal practice for the majority of arthroplasty surgeons in the UK. During the operation, the surgeon may make adjustments to this according to their normal practice in either study arm.

We have developed a CT protocol to minimise the radiation dose, whilst giving the necessary information to use the robot. The total radiation dose for participants in the study (including post-operative imaging, a very small dose of 0.9mSv) has been calculated as 6.1mSv. A total trial dose of 6.1mSv corresponds to a risk of fatal cancer induction of approximately 1 in 3,200 or an increased cancer induction risk of 0.03% and is equivalent to around two years and eight months of exposure to natural background radiation.
This has been discussed with our PPI representatives who reported that they had no objections to the radiation dose and found the percentages easier to understand than the ratio.

The learning curve of the MAKO system is short, as there are a number of similarities to the surgical technique for conventional knee replacements. The primary differences are that the robot constrains the surgeons movements to only allow the cuts to be performed in the pre-planned location, stopping the blade when the edge of the bone has been reached, and that the surgeon has to register the position of the bones to the software at the start of the case, a simple procedure taking approximately 10 minutes.

Our main measure of competence will be the measurement of post-operative alignment. However, stabilisation of surgical time is also an accepted measure of an individual surgeon's learning of a new procedure.(46, 47)

We will ensure that all treating surgeons in the RCT have been trained to use the MAKO system and have performed at least ten previous procedures outside of the trial. We will measure the potential for ongoing learning effects and competence in terms of implant alignment and stabilisation of surgical time, using the process measures described in section 2.2.4.

Surgeons will be eligible to perform RACER trial cases when they have completed the MAKO cadaveric course, have performed ten MAKO cases outside of the trial, and can demonstrate that their surgical time has stabilised (for example, surgical time for last 10 cases). All surgeons in the trial will be expected to perform both intervention and control procedures.

Surgical training will be performed for any surgeon with experience with fewer than ten cases using the MAKO system before they take part in the study. This will involve attendance at a cadaveric knee course and certification of competence based on their performance at the end of the course (this is current practice for all surgeons who wish to use MAKO). Surgeons will also be expected to observe another surgeon in the trial to see a

live surgical case. A learning effects study will be undertaken which will explore the surgical training and learning curve aspect of the trial. More detail on this is provided in section 6.6.

People undergoing robotic arm assisted TKR as part of a surgeon's learning curve (i.e. not in the trial) will be specifically informed that this is the case, an information sheet and consent form will be prepared specifically for this purpose.

Before randomisation, a CRF will be completed documenting the name of the operating surgeon, whether a posterior stabilised, cruciate sacrificing or cruciate retaining implant will be used, whether the patella will be resurfaced, and whether a tourniquet will be used, according to surgeon preference. As these preferences are typically consistent for each surgeon, we will produce a pre-populated form for each surgeon which can be edited if needed, to reduce the burden on the surgeon pre-operatively. This form will be available in electronic and paper forms and will include the date and time of completion of the form to demonstrate that this was performed prior to randomisation.

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 operating surgeon who will perform the procedure will be recorded on the online portal before randomisation to prevent bias due to surgeon seniority, cases should only be done by surgeons who meet the requirements of the study to perform both intervention and control procedures.

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 2.7.3).

2.6.2 Control

The control treatment will be TKR delivered using conventional instruments, using the same Triathlon (Stryker, USA) implants as the intervention. The details of this procedure will also be documented in the RACER surgical manual, as described above. The Triathlon knee replacement is already commonly used in the UK, it is the third most common brand used in the NHS (94,800 recorded cases on the NJR since 2004).(2) As in the intervention arm, all implants will be cemented.

Two additional small incisions will be used to blind to marker placement, these will be identical to the 1cm incisions used for the robotic group and will be covered in the same small dressings. The RACER trial PPI group had no objection to this.

As with the intervention arm, before randomisation, a CRF will be completed documenting the name of the operating surgeon, whether a posterior stabilised, cruciate sacrificing or cruciate retaining implant will be used, whether the patella will be resurfaced, and whether a tourniquet will be used, according to surgeon preference.

These surgical decisions have not resulted in differences in PROM scores between groups in a large UK RCT, but we will monitor this nonetheless to ensure a perceived bias is not introduced by surgeons by making small changes to implant type after the allocation.(11) Where changes occur from the pre-defined plan, the reasons for making these decisions will be recorded on the surgical CRF. Surgeons will be told to be consistent in the use of number of incisions that they use for participants in the study (i.e. they will use the same number of additional incisions for both arms).

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 jigs.

2.6.3 Rehabilitation programme post-surgery

We will use a standardised in-patient and out-patient physiotherapy programme for all participants across both arms of the study. A physiotherapy manual and accompanying materials (including a booklet for participants) will be prepared based current NIHR research led by our lead physiotherapist, Dr Smith (PEP-TALK; NIHR: PB-PG-1216-10010). The programme will be reviewed by the physiotherapy teams across participating 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. The review by participating physiotherapy teams will ensure the programme is deliverable, reflects usual care and does not generate excess treatment costs. This review will be performed remotely via email. If discrepancies between the sites occur, a consensus meeting will be arranged to ensure that agreement is reached on the components of the physiotherapy programme and supplementary paperwork.

A rehabilitation (discharge) booklet will be provided to all participants. This will provide advice about recovering from the TKR, returning to activities and an exercise programme. An equivalent manual will be supplied to site physiotherapists to ensure trial processes are clear and standardised across sites. The booklet and manual will be available on a public website.
Current evidence and NICE draft guidance is that a home exercise plan is best care after TKR and additional physiotherapy sessions do not have impact on outcomes.(48) Despite this, it is common practice in many NHS Trusts to assess patients on their requirement for physiotherapy, and if indicated, refer to out-patient physiotherapy after hospital discharge. The frequency with which this occurs will be recorded. The programme offered in such out-patient settings will mirror that of the patient booklet and physiotherapy manual, 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 physiotherapy components will be reported in line with TIDER and CERT criteria.(49, 50) As a brief overview, our planned rehabilitation package will include:

In-patient

- To begin on the day of, or day following operation and consisting of exercise prescription and gait re-education. All will be provided with a home exercise plan to begin from week zero to the second post-operative week.

- All participants will be provided with a standardised home exercise plan. 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). These will be documented in a home exercise booklet. 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. The adherence of the exercises will be recorded in the participants follow-up questionnaires.

- A member of the physiotherapy team will assess whether a patient requires supervised physiotherapy after discharge. This may be due to reduced knee range of motion, muscle weakness, difficulties in mobilising or functional tasks which more intense, supervised physiotherapy may be deemed as beneficial. Similarly, the referring physiotherapy team member may clinically reason that a patient may not manage self-directed rehabilitation due to motivational reasons, thereby justifying a referral. Interventions offered in such an out-patient setting are itemised below.

Out-patient

- Participants referred to out-patient physiotherapy will be offered four to six sessions (more if clinically required) of physiotherapy provided in a gym setting OR one-to-one OR hydrotherapy as per the physiotherapy teams clinical justification. The uptake of physiotherapy will be collected self-reported as part of health utilisation questionnaire to capture other sources of treatment such as private treatments.
- Participants referred to physiotherapy will also be supported to continue their allocated home exercise as prescribed. (as described above).

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 patients in completing outcomes, such as the post-operative pain scores or at the 12-month follow-up 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. Both of these are already common practice, to preserve sterility and reduce anxiety during the operation. It is recommended that robotic equipment is not removed from theatre unless absolutely necessary.

Additional incisions will be used in the control group to ensure blinding as documented above, the incisions are approximately 1cm. Blinding in surgical trials using sham or placebo incisions is strongly recommended by the Royal College of Surgeons, where it can be achieved.(51, 52) The RACER PPI groups supported this when we presented it to them.

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 online database.

Implant stickers for MAKO consumables, where they are required to be in the notes, will be placed on a sheet inside a blinded envelope before being put in the notes, so this does 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, 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 them not to comment on the presence or absence of visible marker holes on radiographs.

In regards to information to be entered onto the National Joint Registry, surgeons are asked not to select the option whether the Robot was and add RACER study in the comments section without making direct note to which allocation was actually delivered. The true allocation will be confirmed with the NJR after the end of the blinded period to ensure their records are correct.

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. The exception of this is for the closed report for the Data Monitoring Committee, if it is deemed necessary by the committee (otherwise arms for the closed report will be coded).

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 Co-enrolment

Co-enrolment will not normally be recommended, but individual requests can be discussed with the TMG to determine if these will affect the delivery or conduct of the trial.

2.9 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

These have been aligned with the Outcome Measures in Rheumatology (OMERACT) core dataset and have been discussed with our PPI groups to ensure we have chosen appropriate measures, and also understood their relative importance to each other.(53) 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 **Forgotten Joint Score (FJS), 12 months after randomisation**. The FJS is a 12-item patient-reported outcome measure of patient awareness of their joint, it was developed specifically for arthroplasty studies. It demonstrates high test-retest reliability and good convergent validity.(54, 55) It is converted to a score out of 100, with 100 representing the highest (best) score.

The Oxford Knee Score (OKS) is commonly reported in TKR studies but has serious problems with ceiling effects following arthroplasty and will be collected as a secondary outcome. Our PPI group unanimously preferred the FJS to the OKS, when both were presented to them, and any improvement in the OKS may be masked by ceiling effects.(56)

Twelve months has been chosen as the time point for the primary outcome. At this time recovery has plateaued at a level that is typically maintained into the medium to long term.(57, 58) This will ensure our main results are available in a timely manner. We will also capture data at two, five, and 10 years to assess the longer-term outcomes. In particular, in the longer term we will obtain data on implant survival, this is clinically important and can have an important influence on the health economic analysis over longer time horizons.(11)

3.1.2 Secondary outcome measures

In hospital outcomes

- Mean pain intensity, measured using an **11-point numerical rating scale (NRS) for 'pain right now' on the morning of each of the first three days** after surgery. We will also capture pain over the past 24 hours, when the operated knee is at rest and when it is moved. Our PPI groups felt that early post-operative pain was important and recommended a three-day perspective. The NRS scale has been well validated and widely used.(59, 60)
- **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.(61)
- **Opioid use** to the end of day three (total morphine equivalent, using conversion methods established in I-WOTCH, NIHR HTA 14/224/04)
- **Hours from surgery to hospital discharge**.

Post-operative outcomes

The following will be collected at baseline, three, six and 12 months, and two, five and ten years.

- Overall knee function using the **FJS** (54)
- Health utility using **EQ-5D-5L** (this will also be recorded at six weeks) (62, 63)
- Knee-related function using the **OKS,** a 12-item well-validated and widely used score, scored 0-48 (48 being the best score) (56, 64)
- Higher level knee-related function using the **Oxford Activity & Participation Questionnaire (OAPQ)** (65)
- Pain over the last week using the three-item **PROMIS Pain Intensity Scale** (66)
- **Satisfaction with the knee replacement** using a five-point Likert scale (not at baseline) (67)
- **The Participant Global Impression of Change,** a single item, seven-point Likert scale question (not at baseline) **(68)**
- **Re-operations** (not at baseline)
- **Resource** use using participant questionnaires

Safety outcomes

- **Adverse events** related to the operation, the anaesthetic, or the rehabilitation, see section 4 for definitions. Expected adverse events (including serious) will be recorded as outcomes. Serious adverse events will also be reported separately according to the processes in section 4.

3.1.3 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.(11)

3.1.4 Process Measures

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

Surgical measures:

- Time from skin incision to final dressing in minutes.
- Total time in theatre
- Start time of case (i.e. time of day)
- Alignment measures at three months:
  - Rotation and sagittal angles of femoral and tibial components on a focused low-dose CT.(69)
  - Hip-Knee-Ankle angle measured on long-leg alignment x-ray.(70)
- Robot-derived fidelity measures: We will collect the difference between final planned alignment of the leg after intra-operative decisions have been made, and

the achieved result at the end of the procedure (in the coronal plane), this can be measured accurately using the sensors attached to the bones.

Rehabilitation measures:

- Participant self-reporting of physiotherapy visits.

COVID status

- **Covid-19** infection and test confirmation at baseline (i.e., prior COVID infection) and at 3, 6 and 12 month follow-up questionnaires.

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 assessments		✓			
Request pre-operative imaging (planning CT, within 3 months of planned date of surgery)		✓			
Confirm consent prior to surgery			✓		
Randomisation			✓		
Surgery (Intervention/Control)			✓		
Pain NRS (patient reported, site staff administer)		✓		✓	
Opioid use, blood results, time to discharge, theatre timings					✓
PROMs – FJS, OKS, OAPQ, (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. Days)	**6 weeks (±2 weeks) after V2**	**3m (-2 to +6 weeks) After V2**	**6 m (±6 weeks) After V2**	**12 m (± 3m) After V2**	**24m (±6m) After V2**	**5y (±6m) After V2**	**10y (±6m) After V2**
PROMs - FJS, OKS, OAPQ, (paper/electronic)		✓	✓	✓	✓	✓	✓
PROMIS Pain Intensity Scale		✓	✓	✓	✓	✓	✓
Satisfaction & Participant Global Impression of Change		✓	✓	✓	✓	✓	✓
EQ5D (paper/electronic)	✓	✓	✓	✓	✓	✓	✓
Post-operative CT and long-leg x-ray		✓					
OPD review & check PROMS completion				✓			
Resource use		✓	✓	✓	✓	✓	✓
Adverse Events (Complications or re-operations at 2, 5 and 10 years)		✓	✓	✓	✓	✓	✓
End of trial							✓

3.3 Radiological assessments

The radiological assessments 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 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 assess implant rotation, and a long-leg alignment view to assess Hip-Knee-Ankle angle in each site (section 3.1.4). 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. For this appointment, participants will be given a £10 shopping voucher to reimburse travel and parking expenses.

We have developed a CT protocol to minimise the radiation dose, whilst giving the necessary information to use the robot. The total radiation dose for participants in the study (including post-operative imaging, a very small dose of 0.9mSv) has been calculated as 6.1mSv. A total dose within the trial, of 6.1mSv corresponds to a risk of fatal cancer induction of approximately 1 in 3,200 or an increased cancer induction risk of 0.03% and is equivalent to around two years and eight months of exposure to natural background radiation.
This has been discussed with our PPI representatives 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 study 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 knee x-ray series performed, prior to entry into the study. These will be anonymised and transferred using site specific preferred 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 knee replacement
- Any knee or lower limb condition in the same limb as the trial knee.
- 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 12 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.
- Numbness on the lateral side of the surgical wound.
- Early wound oozing which spontaneously resolves.

- Swelling, within the confines of what is considered normal for total knee replacement by the treating clinical team.
- Restriction of range of motion, within the confines of what is considered normal for TKR 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 will be treated as outcomes and reported as such. 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 knee 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 knee pain need to be reported.
- Restriction of range of motion, including manipulation under anaesthetic, arthroscopic or open procedures to relieve stiffness.
- 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 12 months post-randomisation must be recorded on the SAE Form in the participant's CRF and emailed 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 Principal Investigator 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 dedicated study resource account in the first instance. The trial manager will liaise with the investigator to compile all the necessary information. The trial coordinating centre is responsible for reporting any related and unexpected SAEs to the sponsor and REC within required timelines. Events which are conclusively assessed by the Principal Investigators and Chief Investigators as possibly, probably, or definitely related to the trial intervention and are unexpected will be reported to the REC within 15 days.

The EC Medical Devices Directive (93/42/EEC) requires a manufacturer to fully record all adverse incidents that occur during a clinical investigation and include them in the annual reports to the main REC (and MHRA if appropriate). 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 1 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 other 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 and reported to the Sponsor 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 specific 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 reported to the trial team
- 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.

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 overall and by allocation group (which would typically be coded unless the committee requests otherwise) 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 knee 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 and General Data Protection Regulation.

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 Trial Manager in consultation with Chief Investigator, 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 will complete and return the paper CRFs to the RACER trial office. Alternatively sites may be granted access to the database to enter the data remotely directly on the database if they wish to do so. 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 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, although 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 online operation note CRF (mostly online but with paper backup, see section 2.8: 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, it will be collected remotely either by paper CRF given to the participant, by telephone, or by an electronic system (such as the study app).

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.

For radiology assessments (pre- and post-operative CT scans) , see section 3.2 and the related manual. In addition to outcomes specified above, we will also collect radiology images (scans or radiographs) of the knee taken before the participant was recruited and the planning CT to analyse the relationship between pre-operative disease severity and location and clinical outcome. These will be transferred to University Hospitals Coventry and Warwickshire (UHCW) using secure means according to standard NHS procedures and stored anonymously linked to trial number on secure servers accessible only to the trial team.

Participant-reported outcomes will be collected by the central co-ordinating 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.

5.1.3 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 2.6.2).

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.

Text messages will be sent to participants to remind them that their questionnaires are due. In the event of the participant not responding to a questionnaire after a two-week period a second questionnaire will be sent out, a third may also be sent after a further delay. After a third posting we will not post further questionnaires unless requested by the participant (e.g. in the case of issues with the post). If they do not respond to a second posting, then the other data sources collected on the CRF (telephone numbers, email

addresses, next of kin as a last resort only) will be used, unless the participant has indicated previously that these should be used preferentially.

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

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 data will be stored in a designated storage facility within the University Hospitals Coventry and Warwickshire and/or WCTU. Electronic data will be stored on password protected university computers in a restricted access building.

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 ten years without investigator support. 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 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 license fee. Analyses may include individual patient data meta-analyses or other purposes as agreed with the RACER 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 ten years after completion of the trial (ie after the last 10 year follow-up time point).

6. STATISTICAL ANALYSIS

6.1 Power and sample size

The standard deviation for the FJS (range 0-100) is around 30 points.(54, 71) For this study, the target difference is a between group difference of 12 points. Assuming a mean baseline score of 60 points, this equates to a 20% difference in the total score at 12 months, an improvement of one point in each question of the score and a moderate effect size of 0.4. With alpha 5% and power 90%, data are needed from 266 participants to establish this difference. Allowing for up to 20% loss to follow-up the final sample size is **332 participants**.

6.2 Statistical analysis of efficacy and harms

6.2.1 Planned recruitment rate

We have conservatively estimated a **recruitment rate of five/centre/month**. In previous TKR trials we have recruited at 5-13/centre/month (SAFE-TKR, PAKA).

We currently have agreement from seven sites, including the co-CI's centre (Prof Davis), to participate in the study. We anticipate that five sites are needed to if recruiting to this target, but we have obtained agreement from seven sites to ensure we can deliver if a site has difficulty opening. We will not restrict the number of sites, if suitable sites are available then we will consider including them on a case-by-case basis and depending on our progress towards our objectives.

Across the seven sites who have initially agreed to take part over 3400 TKRs were performed in 2017. From a logistics perspective, a site with a single robot could feasibly perform up to 80 cases per month, so capacity to perform robotic cases will not be a restriction. With a staggered start of sites, we anticipate recruitment will take **16 months**.

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 135 consented participants and 38 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% (green) we will continue. If recruitment/randomisation is between 66% and 100% (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.(72) 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 be 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 who are 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/).

6.2.5 Primary outcome analysis

Standard statistical summaries (e.g. medians and ranges or means and variances, dependent on the distribution of the outcome) will be presented for the primary outcome measure and all secondary outcome measures.

The main analysis will investigate differences in the primary outcome measure, the FJS, 12 months after surgery between the two treatment groups on an intention-to-treat basis. The primary analysis will model the FJS using a generalised linear model. Allocation group, age, site, surgeon, gender, BMI (≥35) and primary compartment involved (medial, lateral, or patellofemoral) will be included. Both fixed and random effect models will be used. Sensitivity analyses will be used to explore modelling assumptions, with both fixed and random effect models used.

6.2.3.3 Secondary outcome analysis

Secondary outcomes will be analysed using a similar approach as to the primary outcome appropriate to data type and distribution.

The main secondary outcome for early post-operative pain will be the mean NRS across the first three post-operative days (morning day one to morning day three) as suggested by our PPI group.

Process and fidelity measures will be reported, using an approach appropriate to data type and distribution. A further exploratory analysis will also 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 twelve 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 (< or ≥35)
- Primary compartment involved (medial, lateral, or patellofemoral)

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.

Exploratory models to investigate mediation effects of post-operative joint alignment on FJS (73) and mediation effects of acute post-operative pain on longer term outcome (FJS) whilst accounting for pre-operative pain will also be conducted.(58, 73)

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.(74)

Participants' health service contacts, made in connection with their knee replacement, will be recorded at three, six and twelve 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.(75, 76)

Generic health-related quality-of-life will be assessed at baseline, six weeks, three, six, and twelve months using the EQ-5D-5L questionnaire, and also at two, five and ten 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 https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/technology-appraisal-guidance/eq-5d-5l.(77) 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 within-trial (12 month) incremental cost per QALY estimates and confidence intervals.(78-81) Findings will be analysed and visualised in the cost-effectiveness plane, as cost-effectiveness acceptability curves, net monetary benefit and value of information analysis. If incremental costs and benefits are non-convergent within the trial follow-up then extrapolated modelling will be considered, drawing upon longer term failure rates and sequelae sourced from NJR, ScAP and/or HES.

The 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 TKR using NJR/ScAP data. Modelling would 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. Consequently, a representative and longer-term model will be constructed drawing upon longer-term trial follow-up data and other epidemiological sources. 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.

6.6 Learning effect study

All lead surgeons operating on trial participants will have completed at least ten cases using the robot system before they enrol a patient into the trial. Surgeons who have not reached this threshold will be expected, during their normal practice, to carry out robotic cases to achieve the ten required. In general terms, the procedure for these 'training' cases will follow the normal practice of the Trusts involved when a surgeon is learning a new technique. Thus, the patient will be informed that they are a training case and they will consent specifically for that. This presents an opportunity to study the learning curve associated with the robot, and, therefore, we plan to collect a similar dataset to the trial data, with the exception of the in-hospital pain scores and post-operative CT and x-ray (we do not have funding for these activities in this sub-study).

We will invite clinical teams to provide information about the learning effect study to potential participants and invite them to take part, using the same processes as described above. Participant information sheets and consent forms for this specific purpose will be provided. These people will not be part of the main trial analysis. The sample will be opportunistic based on the needs of the surgeon to have reached the ten cases required so they can take part in the main study. A refusal to take part in the learning effect study will not affect the persons care in any way.

We will be inviting these participants to provide us with outcomes up to 12-months post-surgery, as detailed above; including PROMS and patient clinical records, but not including the in-hospital pain scores, post-operative CT and long-leg x-rays, or two, five and ten year follow-up. They will be monitored for complications and adverse events in the same way as described for the main trial.

Data will be collated and analysed by a clinical research fellow and presented in an appropriate form. Standard statistical summaries (e.g. medians and ranges or means and variances, dependent on the distribution of the outcome) will be presented for process measures, such as duration of surgery, and outcomes such as the FJS at 12-months. The use of quality control metrics such as cumulative sum (CUSUM) and resetting sequential probability ratio (RSPRT) charts will also be explored. Further formal analysis will be defined in a learning effect study specific statistical analysis plan.

7. TRIAL ORGANISATION AND OVERSIGHT

7.1 Sponsor and governance arrangements

University Hospitals of 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 will be managed according to Warwick SOPs, with UHCW SOPs used for contracting and oversight issues.

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 48-months (excluding longer-term follow-up) starting April 2020, the planned timetable is shown below:

Month	Dates	Activity	Milestones
Phase 1: Set up & Internal pilot			
-3-0	Jan 2020 -April 2020	Finalise Protocol HRA/REC submission	Submission to HRA/REC
0-7	April 2020 - Nov 2020	Complete HRA approval Prepare trial materials and CRFs Prepare contracts and plan site-initiation	1st TSC/DMC HRA approval Final versions of all materials approved
7-15	Nov 2020 - Jul 2021	Start recruitment (staggered start of sites). Recruit 135 participants during internal pilot & randomise 38.	Five sites open and recruiting to target 135 participants consented and 38 participants randomised
16	Aug 2021	Assess against stop-go criteria (after 8 months recruitment)	Report to DMC, TSC and HTA
Phase 2: Main trial			
15-23	Jul 2021 - Mar 2022	Complete trial recruitment	332 participants recruited
11-27	Mar 2021 - July 2022	Randomisation (4m delay for waiting lists)	332 participants randomised and surgery performed
23-39	Mar 2022 - July 2023	Complete 12-month follow-up	All 12-month follow-up closed

39-48	July 2023 - April 2024	Data cleaning (3 months) Complete Analysis (4 months) Final data review with DMC/TSC Complete monograph (2 months)	Present results to DMC and TSC Final monograph, and dissemination of results
Phase 3: Long-term follow-up*			
Out of main study period	October 2024, October 2027, and October 2032	Complete 2, 5- and 10-year follow-up (plus 3 months analysis & reporting)	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 or remotely as appropriate.

7.8 Trial Management Group (TMG)

The Trial Management Group, consisting of the project staff, co-investigators and PPI co-investigators involved in the day-to-day running of the trial, will meet every 4 weeks throughout the study period, continuing at lower frequency in the follow-up period (i.e. after 48 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 on page *5-6*.

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 a minimum of two appropriate clinicians and one statistician. The DMC will meet approximately every six months for the duration of the study, although they may choose to meet less frequently when the study is in follow-up.

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 on page 7.
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

A Trial Master File will be set up according to Warwick SOPs and held securely at the coordinating centre.

The coordinating centre will provide 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 3.1.4.

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) will 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)

Patient and public involvement is at the heart of this study. Patients' views have been critical in informing the research and in preparing the proposal. Two of the PPI representatives, Miss Fox, and Mr Grant are co-investigators and both have undergone TKR previously.

Prior to this application we undertook three telephone discussions, and then convened a face-to-face PPI meeting involving six further people who had undergone TKR. Their input helped determine the timing and choice of outcome measures, the study processes and timings, and the way that information should be presented to patients who consider entering the study. Everybody we spoke to agreed that the study was important, they counted any improvement, no matter how small, in better longer-term outcome worthwhile, and they would all have taken part.

Having received the initial feedback from the board, we reconsidered our trial processes and design and, after further discussion with our patient co-applicants, convened a further meeting with four different people who had not heard about the study before. They agreed with the plan and agreed that the 12-month outcome was the most important outcome for them, although they felt that the early pain measures were still worthwhile, and these have been kept as important secondary outcomes. Both groups were happy with the radiation dose from the CT scans and the use of additional incisions for blinding. The feedback of the second group was that although they were happy with blinding, they were clear that they would want to find out about the allocation eventually, our patient co-applicants agreed with that. This has resulted in our decision to inform participants of their allocation after their two-year follow-up point. After two years, we do not anticipate this bringing any substantial bias in into our long-term outcomes.

Miss Fox and Mr Grant, the two patient co-investigators, will be integral to the team, will engage in trial management group meetings and will contribute to trial process and paperwork, including all patient-facing materials and dissemination of the study to a wider audience including patients and the public. Two further patients have agreed to take part and will be invited to be members of the steering committee.

All lay representatives will be supported by the Chief Investigator and the trial team. We have a specific lead for PPI – Dr Rees – who will liaise with the PPI co-investigators. They will have access to training and advice through the UNTRAP network (University/User Teaching and Research Action Partnership), an organisation designed to support PPI activities at the University of Warwick. In addition, researchers within WCTU have developed a training package for lay representatives who wish to be part of TMGs or TSCs which would be available for our PPI representatives.

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 Trial Steering Committee 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 in magazines such as *Arthritis Today*, 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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12. APPENDICES

12.1 Summary of changes

Summary of Changes to Protocol V1.0 29 May 2020			
Page	**Section**	**Previous Wording**	**New wording**
1	Cover	New	Added ISRCTN number Added Ethics Committee Added date of approval
2	Contacts names and numbers		Updated contact details
6	Trial Steering committee members	New	Added PPI members
7	Contact for general queries and supplies	New	Added phone number: Added study resource account email Deleted fax from contacts
11	Trial Title	Robotic Assisted Knee Arthroplasty	Robotic Assisted Arthroplasty
12 and 14	List of abreviations 1.1	New	ADLs - Activities of Daily Living
18	1.3	New	Added additional clarification to the Need for a trial section
19	1.4	New	Addition of the formal research question
19	1.6	two and four additional	two additional
22	2.3	Deleted enrolment	registration onto the study database and baseline data collection.
23	2.3	A screening log will be used at all sites and will be sent to the co-ordinating site monthly (with any identifiers redacted, except trial numbers for participants).	A screening log will be completed at all sites and will be emailed to the co-ordinating centre monthly or completed directly on to the study database (with any identifiers redacted, except numbers for trial participants).
23	2.4	New	Added Section 2.4.1 In-person consent Added Section 2.4.2 Witnessed verbal consent
23	2.4	The investigator or their nominee and the participant must both sign and date the consent form. One copy of this will be kept by the participant, one will be kept by the investigator, and a third will be retained in the patient's hospital record.	The investigator or their nominee and if applicable the independent witness must sign and date the consent form. One copy of this will be posted to the participant, one will be kept by the investigator/nominee, and a third will be retained in the patient's hospital record.
23	2.4.1	New	Added in-person consent section
23	2.4.2	New	Added Witnessed verbal consent
25	2.5.1	New	Randomisation weblink added

Summary of Changes to Protocol V1.0 29 May 2020			
Page	**Section**	**Previous Wording**	**New wording**
28	2.6.1	Sub-Study	Learning Effects study
28	2.6.1	Before randomisation, a CRF will be completed documenting the name of the operating surgeon, whether a posterior sacrificing or retaining implant type will be used, whether the patella will be resurfaced, and whether a tourniquet will be used, according to surgeon preference	Before randomisation, a CRF will be completed documenting the name of the operating surgeon, whether a posterior stabilised, cruciate sacrificing or cruciate retaining implant will be used, whether the patella will be resurfaced, and whether a tourniquet will be used, according to surgeon preference.
28	2.6.2	Two or four	Two additional
28	2.6.2	As with the intervention arm, before randomisation, a CRF will be completed documenting the name of the operating surgeon, whether a posterior sacrificing or retaining implant type will be used…	As with the intervention arm, before randomisation, a CRF will be completed documenting the name of the operating surgeon, whether a posterior stabilised, cruciate sacrificing or cruciate retaining implant will be used
28	2.6.2	We will also confirm the number of incisions that the surgeon will make for marker placement (two, or no additional scars, i.e., all markers within the wound) before randomisation	Surgeons will be told to be consistent in the use of number of incisions in the study (i.e. they will use the same number of additional incisions for both arms).
30	2.6.3	The adherence of the exercises will be recorded in a home exercise log for the six weeks from discharge	The adherence of the exercises will be recorded in the participants follow-up questionnaires.
30	2.6.3	Exercise plan	Exercise as prescribed
31	2.7.1	New	In regards to information to be entered onto the National Joint Registry, surgeons are asked not to select the option whether the Robot was and add RACER study in the comments section without making direct note to the Robot. The true allocation will be confirmed with the NJR after the end of the blinded period to ensure their records are correct.
31	2.7.2	New	The exception of this is for the closed report for the Data Monitoring Committee, if it is deemed necessary by the committee (otherwise arms for the closed report will be coded).
34	3.1.4	New	**Covid-19** infection and test confirmation at baseline (i.e., prior COVID infection) and at 3, 6 and 12 month follow-up questionnaires.

Summary of Changes to Protocol V1.0 29 May 2020			
Page	**Section**	**Previous Wording**	**New wording**
36	3.2	New	Added outcome measures to table (PROMIS and PGIC) and complications collected at 2, 5 and 10 years)
40	4.2	SAEs to be faxed	SAEs to be emailed to the sponsor
41	4.2	Events which are possibly, probably, or definitely related to the trial intervention and are unexpected will be reported to the REC within 15 days.	Events which are conclusively assessed by the Principal investigators and chief investigators as possibly, probably, or definitely related to the trial intervention and are unexpected will be reported to the REC within 15 days.
43	5.1.1	New	Alternatively sites may be granted access to the database to enter the data remotely directly on the database if they wish to do so.
46	5.1.2	For radiology assessments, see section 3.2 and the trial manual.	For radiology assessments (pre- and post-operative CT scans) , see section 3.2 and the related manual.
49	6.2.1	Six sites	Number or sites adjusted to seven
52	6.6	Sub-study	Learning effect study
56	7.7	New	**Added "**or remotely as appropriate".
		Throughout the document, correction of typos, minor clarifications	