

# BMJ Open Robotic Arthroplasty Clinical and cost Effectiveness Randomised controlled trial (RACER-knee): a study protocol

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## ABSTRACT

**Introduction** Robotic-assisted knee replacement systems have been introduced to healthcare services worldwide in an effort to improve clinical outcomes for people, although high-quality evidence that they are clinically, or cost-effective remains sparse. Robotic-arm systems may improve surgical accuracy and could contribute to reduced pain, improved function and lower overall cost of total knee replacement (TKR) surgery. However, TKR with conventional instruments may be just as effective and may be quicker and cheaper. There is a need for a robust evaluation of this technology, including cost-effectiveness analyses using both within-trial and modelling approaches. This trial will compare robotic-assisted against conventional TKR to provide high-quality evidence on whether robotic-assisted knee replacement is beneficial to patients and cost-effective for healthcare systems.

**Methods and analysis** The Robotic Arthroplasty Clinical and cost Effectiveness Randomised controlled trial-Knee is a multicentre, participant-assessor blinded, randomised controlled trial to evaluate the clinical and cost-effectiveness of robotic-assisted TKR compared with TKR using conventional instruments. A total of 332 participants will be randomised (1:1) to provide 90% power for a 12-point difference in the primary outcome measure; the Forgotten Joint Score at 12 months postrandomisation. Allocation concealment will be achieved using computer-based randomisation performed on the day of surgery and methods for blinding will include sham incisions for marker clusters and blinded operation notes. The primary analysis will adhere to the intention-to-treat principle. Results will be reported in line with the Consolidated Standards of Reporting Trials statement. A parallel study will collect data on the learning effects associated with robotic-arm systems.

**Ethics and dissemination** The trial has been approved by an ethics committee for patient participation (East Midlands—Nottingham 2 Research Ethics Committee, 29 July 2020. NRES number:

## STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ Large, multicentre, randomised controlled trial of robotic-assisted total knee arthroplasty compared with total knee arthroplasty with conventional instruments.
- ⇒ Participant-assessor blinded, including sham incisions for marker clusters and blinded operation note.
- ⇒ Embedded learning study to assess outcomes of surgeons training with the robotic system.
- ⇒ Clinical outcomes assessed using primary outcome measure of Forgotten Joint Score as well as a range of early and late secondary outcome measures.
- ⇒ Cost-effectiveness evaluated with built in health economic evaluation using both within-trial and modelling approaches (if within-trial analysis does not show convergence or dominance) to analyses.

20/EM/0159). All results from the study will be disseminated using peer-reviewed publications, presentations at international conferences, lay summaries and social media as appropriate.

**Trial registration number** ISRCTN27624068.

## INTRODUCTION

Robotic-assisted knee replacements are increasingly common worldwide, with little high-quality evidence as to whether they are clinically or cost-effective.<sup>1</sup> Total knee replacements (TKR) are one of the most common orthopaedic procedures, with over 100 000 performed annually in the UK at a cost of more than £550 million.<sup>2</sup> While TKR offers good improvements in pain and function for most people, the majority have some ongoing restriction and around 15%–20% have chronic pain or are not satisfied with their knee replacement.<sup>3–9</sup>

Surgeons are increasingly looking to use new technologies during TKR surgery in the hope that they may improve results and reduce variation in outcomes. The MAKO robotic arm assisted system uses CT scanning to create a three-dimensional model of the person's knee to plan and programme the system to deliver cuts to the bone.

The causes of poor function, persisting pain and dissatisfaction after TKR are likely to be multifactorial. It is proposed that some of these factors could be improved with better surgical technique and precision.<sup>10–16</sup> Robotic-assisted cuts may be more accurate and consistent.<sup>17</sup> This allows surgeons to make small adjustments to implant position to improve the tension of surrounding ligaments during the operation, although the value of this in terms of clinical outcome is unknown. The robotic arm provides haptic constraint to the surgeon potentially reducing damage to the surrounding soft tissues. This may reduce surgical trauma, in turn reducing postoperative pain and facilitating earlier discharge.<sup>18–20</sup>

Conventional instruments have been in use for decades and are well understood by surgeons. It may be that the conventional approach is already sufficiently accurate and provides outcomes that are as good, or better than robotic systems. It is also possible that the changes in implant positioning undertaken by surgeons using robotic assistance are not beneficial. Conventional surgery does not require drilling holes in the femur and tibia for marker placement which could be painful and introduces a small risk of fracture.<sup>21</sup> Robotic arm-assisted surgery comes with added expense including robotic hire costs, dedicated single-use equipment for each case and imaging costs. Mitigating these costs would require a reduction in hospital length of stay, a reduction in future revisions or large differences in health utility in favour of robotic-assisted surgery. Therefore, uncertainty remains about whether surgery with conventional instruments or robotic-assisted surgery is the best approach for TKR in terms of clinical outcomes for people, or in terms of cost-effectiveness for policy-makers.

There is limited evidence from a short-term study comparing costs between robotic arm-assisted and conventional surgery from a health payer perspective, which found a potential reduction from robotic arm-assisted surgery, although this was based on a strong assumption that hospital length of stay could be reduced.<sup>22</sup> Another cost-effectiveness study showed that robotic-arm assisted surgery could be cost-effective at a high volume for the health service.<sup>23</sup> However, these evaluations require high-quality data to underpin their assumptions and provide a robust answer to whether robotic-assisted surgery is worthwhile.

For this study, we have chosen to evaluate the MAKO robotic system. At the time of writing, this is the most commonly used robotic arthroplasty system worldwide. MAKO was, up to 2019, the only semiactive robotic-arm system available to the National Health Service (NHS) (MAKO, Stryker, USA). While other robotic-arm systems

are becoming available, they are earlier in their development and clinical testing.<sup>24</sup> Worldwide use of the MAKO robot is growing rapidly. Between 2017 and 2018, there has been a greater than threefold increase in MAKO cases, and over 500 000 TKRs have now been done using MAKO globally (Personal communication, Michael Ormond, Stryker, 2022). The technology has been stable over this time and is not expected to change in the near future.

### Robotic surgery for TKR: existing knowledge

A 2020 systematic review and meta-analysis of 22 studies with 2346 participants assessing robotic systems for TKR identified no randomised controlled trials (RCTs) using the MAKO system.<sup>25</sup> Many of the included studies were either prospective or retrospective case series. These studies did not contain well-defined follow-up points or consistent outcomes and a meaningful meta-analysis could not be performed. Nevertheless, a small positive effect on a range of clinical outcomes was observed.

There have been limited studies reporting the use of MAKO for TKR. A 2018 UK non-randomised comparative study found early benefits from robotic-assisted TKR using MAKO (N=40) compared with conventional instruments (N=40). These included reduced pain and earlier discharge.<sup>18</sup> A small RCT showed reduced early postoperative inflammatory response.<sup>26</sup> This early reduction in postinflammatory response was further confirmed by a small retrospective study.<sup>27</sup> 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 at 6 months.<sup>28</sup> A 2016 UK randomised trial (N=139) compared accuracy of bone cuts between partial knee replacement with the MAKO system, and conventional instruments with a different implant design.<sup>29</sup> Bone cuts were more accurate with robotic surgery and while clinical outcomes (including the Forgotten Joint Score (FJS) and the Oxford Knee Score (OKS)) were similar at 2 years, there were non-significant differences favouring robotic systems in some clinical outcomes (including early pain and the FJS) at 1 year.<sup>29</sup> The potential benefits for TKR, a larger procedure involving more soft tissue exposure and with more heterogeneous levels of satisfaction, might be expected to be greater.

The available evidence on MAKO is limited to small, randomised trials and non-randomised studies which lack medium-term to long-term follow-up at well-defined time points using patient-reported outcomes. A definitive trial of the MAKO robot is now both needed and timely.

### Aim

The overarching aim is to determine whether robotic-assisted TKR or manual TKR with conventional instruments are more clinically and cost-effective in a UK healthcare setting.

## Research question

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

## Objectives

### Primary objectives

- ▶ To compare robotic-assisted TKR against TKR performed with conventional instruments using the FJS, 12 months after randomisation.
- ▶ To determine the cost-effectiveness of robotic-assisted TKR in a UK setting.

### Secondary objectives

- ▶ To compare differences in pain in the first 3 days after surgery, estimated blood loss, analgesic use and time to discharge between groups.
- ▶ To compare the FJS, OKS, Oxford Activity & Participation Questionnaire (OAPQ), EuroQol-5 Dimension 5-Level (EQ-5D-5L), pain intensity, satisfaction, participant impression of change, adverse events (AEs), reoperation and implant survival at 3, 6 and 12 months and 2, 5 and 10 years following surgery.

## METHODS

### Trial design

The Robotic Arthroplasty Clinical and cost Effectiveness Randomised controlled trial (RACER-knee) is a multi-centre, participant-assessor blinded, individually RCT to evaluate the clinical and cost-effectiveness of robotic-assisted TKR compared with conventional TKR in the UK healthcare setting. In the Idea, Development, Exploration, Assessment, Long-term monitoring (IDEAL) classification, this represents a stage 3 study.<sup>30</sup>

### Ethics and dissemination

The trial received full ethical approval on 29 July 2020 from the East Midlands—Nottingham 2 Ethical Review Board (NRES number: 20/EM/0159). The trial is being undertaken in accordance with guidance from the Declaration of Helsinki and Good Clinical Practice guidelines; and following Warwick Clinical Trials Unit (WCTU) Standard Operating Procedures (SOPs). Oversight will be provided by an independent data monitoring committee (DMC) and a trial steering committee (TSC). Both groups will comprise independent members in line with the relevant WCTU SOPs and National Institute for Health and Care Research (NIHR) guidelines. A monitoring plan will be implemented by the study co-sponsors. Protocol amendments will be communicated to study sites by the co-ordinating team.

The results of the trials will be reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines.<sup>31</sup> Final results will be submitted to a peer-reviewed clinical journal and presented as national and international meetings such as the British Orthopaedic Association and the American Academy of Orthopaedic Surgeons. In all publications, authorship will follow the guidance from the International Committee of

Medical Journal Editors. Investigators will share deidentified data and code used to develop the results on request to the chief investigators or WCTU subject to formal mutually agreed data sharing agreements being in place.

We will work closely with our patient and public involvement (PPI) representatives to identify routes to dissemination to the public, and ensure dissemination to participants and the wider public is undertaken appropriately. Lay summaries and infographics will be published on the trial website, social media and in conjunction with the main publication if policies allow.

### Trial registration and study dates

The trial is registered with the ISRCTN register (number: 27624068). The current version of the protocol is V3.0 dated 26 November 2021. The study opening date was April 2020 with a planned end date for the main trial in April 2024, with long-term follow-up continuing potentially until October 2032.

### Outcome measures

The choice of outcome measures was made in collaboration with our PPI partners to ensure we selected measures important and appropriate to potential participants.

### Primary outcome

The primary clinical effectiveness outcome is the FJS collected 12 months after randomisation.<sup>32</sup> The FJS is a participant-reported outcome measure developed specifically for arthroplasty research. A score of 0–100 is generated, 100 representing the best score. The 12-item scale has demonstrated good reliability and convergent validity.<sup>33 34</sup> Twelve months will be the primary outcome time point as recovery after TKR has been demonstrated to plateau by this point and is maintained into the medium to long term.<sup>35</sup>

### Secondary outcomes

#### Early outcomes

- ▶ Mean pain intensity, measured using an 11-point Numerical Rating Scale (NRS) for ‘pain right now’ on the morning of days 1, 2 and 3 after surgery. The NRS has been well validated and widely used.<sup>36 37</sup>
- ▶ Pain over the past 24 hours, when the operated knee is at rest and when it is moved, collected as above on the first 3 days.
- ▶ Estimated blood loss calculated using Brecher’s formula, based on preoperative and post-operative Haematocrit measurements from routinely taken clinical blood measurements, and volume, if any, of blood transfused.<sup>38</sup>
- ▶ Opioid use to the end of day 3 as total morphine equivalent dose, using conversion methods established in a WCTU study on opioid reduction.<sup>39</sup>
- ▶ Hours from end of surgery to hospital discharge.

#### Participant-reported outcomes

All collected at baseline (prerandomisation); 3, 6, 12 months and 2, 5 and 10 years postrandomisation.

- ▶ Overall knee function using the FJS.
- ▶ Health utility using EQ-5D-5L (additionally recorded at 6 weeks).<sup>40 41</sup>
- ▶ Knee-related function using the OKS, a 12-item well-validated and widely used score.<sup>42 43</sup>
- ▶ Higher level knee-related function using the OAPQ.<sup>44</sup>
- ▶ Pain over the last week using the three-item Patient-Reported Outcomes Measurement Information System (PROMIS) Pain Intensity Scale.<sup>45</sup>
- ▶ Satisfaction with the knee replacement using a five-point Likert scale (not at baseline).<sup>46</sup>
- ▶ The Participant Global Impression of Change, a single item, seven-point Likert scale question (not at baseline).<sup>47</sup>
- ▶ Reoperations and complications (not at baseline), categorised into revision procedures using the National Joint Registry definition and other reoperations.<sup>2</sup>
- ▶ Resource use using participant questionnaires (not at baseline).
- ▶ Resource use using NHS datasets (only at 5 and 10 years).

#### Safety outcomes

- ▶ AEs related to the operation, the anaesthetic or the rehabilitation. Expected AEs (including serious) will be recorded as outcomes. Serious AEs (SAEs) will be collected according to relevant WCTU SOPs.

#### Process measures

##### 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.
- ▶ Hip-Knee-Ankle angle measured on long-leg alignment x-ray.
- ▶ 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.
- A bespoke database management system has been developed by an experienced programming team at WCTU, with a detailed data management plan prepared in-line with WCTU SOPs to maintain high-quality data for the duration of the trial.

#### Eligibility criteria

##### Inclusion criteria

1. Osteoarthritis of the knee with pain, disability and changes on standard of care clinical images (plain radiographic or MRI according to normal clinical

practice) that, in the opinion of the treating clinician, warrants TKR.

2. Conservative therapy has been unsuccessful, as judged by the treating clinician.<sup>48</sup>

##### Exclusion criteria

3. Osteoarthritis secondary to inflammatory arthropathy or intra-articular fracture, as determined by the treating clinician.
4. 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.
5. Age <18 years.
6. Unfit for TKR, or surgery is otherwise contraindicated (eg, concurrent infection).
7. Previous randomisation in the present trial for the other knee.
8. Unable to take part in trial processes, including people unable to communicate or complete questionnaires in English, or people unable to give informed consent.

#### Participant identification

Potential participants will be identified by clinical teams using three approaches: intermediate or secondary care clinic referrals; preoperative education classes and/or surgical waiting lists. The attending clinician will confirm eligibility based on their clinical assessment and standard care preoperative imaging. Monthly screening logs will be completed at each site recording all screened participants. If suitable for inclusion, potential participants will be given information about the trial and instructed to discuss with a member of the research team if needed. Information sheets will be posted or emailed. A member of the research team will then carry out the informed consent process, participant registration and baseline data collection.

Prior to randomisation on the day of surgery, consent and eligibility will be reviewed with the participant. Baseline data which are more than 6 months old will be collected again prior to randomisation.

#### Randomisation and treatment allocation

Randomisation will be done after the eligibility and consent review has taken place. Participants will be randomly allocated up to 3 hours prior to the planned start time of their procedure. This will allow theatre staff time to prepare for robotic surgery but not to change the surgical list order based on the allocation.

Participants will be randomly allocated on a 1:1 basis to two treatment groups using a computer-based randomisation system designed by WCTU programming team. A minimisation algorithm with a 70% random factor will be designed to determine the allocation, with factors for age (<60 years, ≥60 years), recruiting site, surgeon, body mass index (BMI) (<35, ≥35) and primary compartment involved (medial, lateral or patellofemoral).<sup>49</sup>

Randomisation will be sequential at site level and the order of the list will not be changed due to a specific allocation. Participants will be identified using local site arrangement, such as stickers on clinical notes, to flag inclusion in the trial without recording individual allocations.

Due to the delay between randomisation and the procedure start time, there is a small chance that participants may become ineligible during that time (such as a medical event prior to the operation). In cases where this happens, to maintain participant blinding, if surgery can proceed within 72 hours of randomisation, then the participant will receive their surgery as allocated. If the participant cannot receive treatment within 72 hours, they will be removed from the study and classified as 'became ineligible between randomisation and intervention'. These randomisations will not be used in the intention-to-treat analysis and will be reported separately in the CONSORT chart at the end of the study. If they wish to participate later, they will be reregistered and receive a new treatment allocation.

Participants in the study are free to withdraw from follow-up at any time with no prejudice or effect on their current care. All withdrawals will be monitored by the Trial Management Group and oversight committees.

### Trial interventions

#### Group 1: robotic TKR (intervention)

Participants allocated to the intervention treatment will receive TKR delivered using the MAKO robotic system and Triathlon implants (Stryker, USA). All implants will be cemented. Participants from both groups will have a CT scan in line with the needs of the MAKO system typically no more than 12 weeks prior to the date of surgery. If surgery is delayed, then the surgeon will make a clinical decision whether to use current CT scans or repeat the scan.

A protocol will be used to minimise radiation exposure from the study CT scans. The total dose in the study has been calculated as 6.1 mSv. This corresponds to an increased cancer induction risk of 0.03% and is equivalent to around 2 years and 8 months of exposure to natural background radiation. This has been discussed with our PPI representatives who reported that they had no objections.

All treating surgeons will be expected to deliver both intervention and control procedures and will have been trained to the use the MAKO system on at least 10 cases prior to any trial involvement.

Full details of the procedure will be documented in the RACER-knee surgical manual. While the initial plan will be to achieve mechanical alignment, surgeons may choose to make adjustments as they normally would in their routine clinical practice. All other care, including anaesthesia and postoperative analgesia, will be according to standard care.

#### Group 2: conventional TKR (control)

Participants allocated to the control group will receive TKR delivered using conventional instruments and the same Triathlon implants as the intervention group. As

with the robotic surgery, while the initial strategy will be to achieve mechanical alignment, surgeons may choose to make adjustments as they normally would in their routine clinical practice. Patient-specific instruments or computer navigation will not be used. The RACER-knee surgical manual will also describe the full details of the procedure. All implants will be cemented.

Two small incisions of 1 cm will be used to blind to marker placement; identical to incisions used for the robotic group and covered with the same small dressings.

### Rehabilitation

A standardised programme of inpatient and outpatient physiotherapy has been developed for participants in both arms of the study. In accordance with National Institute for Health and Clinical Excellence (NICE) guidance, this includes standardised postoperative information, home exercise plans and the potential for supervised physiotherapy as required, based on the standard approach and assessment for the recruiting site.<sup>50</sup> In addition, a physiotherapy manual and booklet for participants has been prepared. A rehabilitation booklet will be provided to all participants with advice about recovery, return to activities and exercise. All materials have been developed in line with best current evidence and NICE guidance.<sup>50</sup> The physiotherapy components will be reported in line with Template for Intervention Description and Replication (TIDieR) and Consensus on Exercise Reporting Template (CERT) criteria.<sup>51 52</sup>

### Blinding

Participant and assessor blinding will be maintained throughout the study. Any research staff collecting participant outcomes will be considered assessors, and clinical staff at all sites will be trained in the importance of maintaining blinding. Participants will report which treatment they think they received at the 12-month primary outcome data collection time point. At the request of the PPI group, participants will be informed of their treatment after they have completed the 2 years follow-up.

Hospital staff will be trained to not divulge treatment allocations either verbally or on theatre lists. Drapes and headphones will be used in theatre to maintain blinding if needed, both of which are common practice to preserve sterility and ease nervousness. Sham incisions of approximately 1 cm will be used in the control group to maintain participant blinding, which received strong support from the study PPI group during the study design phase. Blinding in surgical trials using sham incisions is strongly recommended by the Royal College of Surgeons.<sup>53</sup>

A customised operation note, based on previous experience in the START:REACTS study, has been designed to ensure that intraoperative data collection regarding the robot is not a weak point in maintaining blinding.<sup>54</sup> Participants in both groups will have standardised written templates containing no details regarding the robotic system, and details of the use of the robot will be recorded by the surgeon in a simple online form. Any information

on MAKO consumables used will be placed in a blinded envelope before being put in the notes.

Unblinding will be a rare event and should only happen in medical emergencies when knowledge of treatment allocation is needed for clinical management of a participant. We do not anticipate that knowledge of the treatment allocation will influence any urgent clinical management in this setting, hence no formal unblinding process will be developed. If unblinding is required for any reason, the trial team are to be contacted directly.

### End of trial

The trial will end when the final follow-up data have been received and entered, and no additional follow-up activities are planned. The trial will only be stopped prior to this if mandated by the Research Ethics Committee (REC), the MHRA, the TSC or if funding for the trial ceases. The REC will be notified within 90 days of trial closure.

### Patient and public involvement

PPI will be at the centre of this trial; their views have been key in informing the research and preparing the study. A six-person group who had experience of TKR helped determine study timelines, outcomes and processes at the development stage. They reviewed participant facing materials and recommended the timing of the primary outcome data collection. Two PPI representatives will attend monthly trial management meeting and another two will attend and contribute to the TSC meetings. We have a lead PPI coinvestigator who is responsible for liaising with PPI coinvestigators.

### Learning effects study

The parallel learning effects study is an opportunity to study the learning curve associated with the use of the robot. Surgeons who have not reached 10 MAKO cases will not be able to register and enrol participants into the trial. Surgeons will need to achieve the 10 learning cases in their normal practice, and participants will be informed that they are a training case and will be required to provide specific consent to take part in the learning study. They are not part of the main study, but we will invite these participants to provide us with the same set of outcomes used for the randomised trial, up to 12 months postsurgery.

The data will be analysed as a separate work package from the main randomised trial and further details will be defined in a learning effect study specific analysis plan.

### Safety reporting, AE, SAEs

All AEs, SAEs, serious adverse device events (SADEs) and unanticipated SADEs will be defined using widely accepted standard criteria. For this study, AEs will be recorded for events that occur during the in-patient stay and up to 12 months postrandomisation and are thought to be related to the trial interventions or the condition under study. This may include any events related to anaesthetic, physiotherapy or other trial processes. A

list of expected AEs will be produced and be treated as outcomes and reported as such.

Information on AEs and SAEs occurring from the date of randomisation up until 12 months postrandomisation will be collected. The cosponsor (WCTU) will be notified within 24 hours of the research staff becoming aware of the event. All events will be followed up until the event has been resolved and an outcome has been agreed.

### Statistical analysis

#### Sample size

The sample size calculation was based on the primary outcome measure, the FJS, which has a range of 0–100. A target difference of 12 points was chosen with an assumed SD of 30 points based on estimates taken from two population-based studies.<sup>34 55 56</sup> This resulted in a 20% difference in total score at 12 months and a moderate effect size of 0.4. For power of 90% and a two-sided type I error rate of 5%, 266 participants are needed. After allowing for up to 20% lost to follow-up, the required sample size is 332 participants.

#### Statistical analysis plan

All analyses will be reported in accordance with the CONSORT guidelines.<sup>31</sup> A comprehensive statistical analysis plan will be agreed with the DMC prior to any formal analysis. Baseline data will be presented to check comparability of treatment arms. All descriptive data will be summarised using standard statistical methods (eg, means and SDs for continuous data).

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 ( $\geq 35$ ) 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. Secondary outcomes will be analysed using a similar approach as to the primary outcome appropriate to data type and distribution, including revision surgery rates and reoperation rates between treatment groups. As a further secondary outcome, we will report modified FJS and OKS scores, rescaled using item response theory methods with the intention of improving the efficiency of the measures.

Missing data will be scrutinised 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.

Prespecified subgroup analyses will be undertaken to investigate whether the intervention effect differs between:

- ▶ BMI group ( $< 35$  or  $\geq 35$ ).
- ▶ Primary compartment involved (medial, lateral or patellofemoral).

The models will follow methods of primary analysis with additional interaction terms included in the regression model. These will be exploratory analyses only and subsidiary to the primary analysis.

### Health economic analysis

A prospectively planned economic evaluation will be conducted from an NHS and personal social services perspective, according to the recommendations of the NICE reference case.<sup>57</sup>

Participants' health service contacts, made in connection with their knee replacement, will be collected at all follow-up time points. Time lost from work (paid/unpaid) will also be recorded. Differences in index surgical procedures will be explored through changes in use of surgical time and facilities. Healthcare resource use will be costed using most recently available published national reference costs, reflatd to a common year.<sup>58</sup>

Generic health-related quality of life will be assessed using the EQ-5D-5L questionnaire. 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. Using the trapezoidal rule, the area under the curve of health status scores will be calculated, providing patient-level (quality-adjusted life year) 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 months) incremental cost per QALY estimates and CIs.<sup>59–61</sup> Findings will be analysed and visualised in the cost-effectiveness plane, as cost-effectiveness acceptability curves, net monetary benefit and value of information analysis.

The limitation of trial-based economic analyses of emergent technologies is that they may not accurately represent real costs of use. Use of the robot is typically through a monthly hire cost, with cost per procedure dependent on hospital throughput and the hire charge. Additionally, the costs of technologies can change in response to market conditions. Sensitivity analysis will explore these issues. Cost-effectiveness analyses will be limited to within-trial data if differences in costs and outcomes are convergent or if either surgical path is robustly dominant in the first 12 months. If not, then a longer-term model will be constructed using longer-term trial follow-up data and other epidemiological sources.

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**Contributors** AM and ETD first identified the clinical question and act as joint chief investigators and main grant holders for the RACER-Knee study. MJB, NDC, DD, NF, DRE, NF, FSH, CEH, JM, HP, AM and ETD are co-applicant grand holders and are responsible for the design of the RACER-Knee study. These authors contributed to the development of the main trial protocol, the draft of this manuscript and approval of the final version. JF and NJG are patient representatives as well as co-applicants on the grant and provided expertise from their perspectives. JG, ETD, HP, EGM, CK, DRE, MJB, NDC, DD, NF, JF, NJG, FSH, CEH, JM, BM, CEHS, TOS, JAS, ADT, SR, MU and AM contributed to the development of the main trial protocol, in addition to contributing to the writing of the manuscript and approval of the final version. JG led the first draft of the manuscript, submitted the first draft of this manuscript and acted as corresponding author during the review process. This protocol was written following the SPIRIT protocol guidance.

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**Competing interests** Stryker is providing funding for consumables, preoperative CT costs and 10 min of theatre time, according to contractual arrangements. They also fund some postoperative CT costs in the learning effects study. Appropriate contracts are in place to ensure the independence of the trial team with regard to study design, data collection, management, analysis and interpretation in line with NIHR reporting standards. Multiple investigators are investigators on two other NIHR-funded studies receiving additional support for treatment costs from Stryker, START:REACTS (16/61/18) (AM, HP, CEH, JM and MU) and RACER-Hip (NIHR131407) (AM, ETD, HP, SR, CEH, DRE, JM, FSH, JAS and MU). The full independence of the investigators of these related studies are protected by legal agreements, similar to this study. FSH receives funding from Stryker to run clinical studies. Multiple authors report other unrelated research grants from NIHR during the conduct of the study. DRE, HP and JG are supported from NIHR Research Capability Funding via University Hospitals Coventry and Warwickshire. MU is chief investigator or coinvestigator on multiple previous and current research grants from the UK National Institute for Health Research, Arthritis Research UK and is a coinvestigator on grants funded by the Australian NHMRC and Norwegian MRC. He was an NIHR Senior Investigator until March 2021. He has received travel expenses for speaking at conferences from the professional organisations hosting the conferences. He is a director and shareholder of Clinivivo that provides electronic data collection for health services research. He is part of an academic partnership with Serco Ltd, funded by the European Social Fund, related to return to work initiatives. Until March 2020 he was an editor of the NIHR journal series, and a member of the NIHR Journal Editors Group, for which he received a fee.

**Patient and public involvement** Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

**Patient consent for publication** Not applicable.

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