BMJ Open

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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-068255
Article Type:	Protocol
Date Submitted by the Author:	12-Sep-2022
Complete List of Authors:	Griffin, James; University of Warwick Warwick Clinical Trials Unit, Warwick Medical School; University Hospitals Coventry and Warwickshire NHS Trust Davis, ET; Royal Orthopaedic Hospital NHS Foundation Trust Parsons, Helen; University of Warwick Warwick Clinical Trials Unit, Warwick Medical School; University Hospitals Coventry and Warwickshire NHS Trust Gemperle Mannion, Elke; University of Warwick Warwick Clinical Trials Unit, Warwick Medical School Khatri, Chetan; University of Warwick Warwick Clinical Trials Unit, Clinical Trials Unit; University Hospitals Coventry and Warwickshire NHS Trust Ellard, David; University of Warwick Warwick Clinical Trials Unit, Warwick Medical School; University Hospitals Coventry and Warwickshire NHS Trust, Blyth, MJ; Glasgow Royal Infirmary, Orthopaedic Research Unit, Department of Trauma and Orthopaedics Clement, Nicholas; Royal Infirmary of Edinburgh, Orthopaedics and Trauma; University of Edinburgh Division of Clinical and Surgical Sciences, Orthopaedics Deehan, David; Newcastle Upon Tyne Hospitals NHS Trust Flynn, Nicholas; Portsmouth Hospitals NHS Trust Fox, Josephine; Patient Representative Grant, Nicholas; Patient Representative Haddad, Fares; University College London Hospitals NHS Foundation Trust Hutchinson, Charles; University of Warwick Warwick Medical School, Warwick Medical School; University Hospitals Coventry and Warwickshire NHS Trust Mason, James; University of Warwick Warwick Clinical Trials Unit, Warwick Medical School Mohindru, Bishal; University of Warwick Warwick Clinical Trials Unit Scott, Chloe; Royal Infirmary of Edinburgh, Orthopaedics; University of Edinburgh Division of Clinical and Surgical Sciences, Smith, Toby; University of East Anglia, Faculty of Medicine and Health Sciences; University of Oxford, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences Skinner, John; Royal National Orthopaedic Hospital NHS Trust Toms, Andrew ; Royal Devon and Exeter NHS Foundation Trust Rees, Sophie; University of Bristol, Bristol Trials Centre Underwood, Martin; University of Warwick Warwick Clinical Trials Unit,

	Warwick Medical School; University Hospitals Coventry and Warwickshire NHS Trust Metcalfe, Andrew; University of Warwick Warwick Clinical Trials Unit; University Hospitals Coventry and Warwickshire NHS Trust
Keywords:	ORTHOPAEDIC & TRAUMA SURGERY, Knee < ORTHOPAEDIC & TRAUMA SURGERY, Adult orthopaedics < ORTHOPAEDIC & TRAUMA SURGERY, Adult surgery < SURGERY

The Robotic Arthroplasty Clinical and cost Effectiveness Randomised controlled trial (RACER-knee): a study protocol.

Mr J Griffin[a,c], Professor ET Davis[b], Dr H Parsons[a,c], Mrs E Gemperle Mannion[a], Mr C Khatri[a,c], Professor DR Ellard[a,c], Mr M Blyth[d], Mr ND Clement[e], Mr D Deehan[f], Mr N Flynn[g], Miss J Fox[h], Mr N Grant[h], Mr FS Haddad[i], Professor CE Hutchinson[c,j], Professor J Mason[a], Dr B Mohindru[a], Ms CEH Scott[e], Dr TO Smith[k], Professor J Skinner[l], Professor AD Toms[m], Dr S Rees[n], Professor M Underwood[a,c], Mr AJ Metcalfe[a,c]

[a]Warwick Clinical Trials Unit, Warwick Medical School, University of Warwick, UK.

[b]The Royal Orthopaedic Hospital NHS Foundation Trust, Birmingham, UK.

[c]University Hospitals Coventry and Warwickshire NHS Trust, Coventry, UK

[d]Glasgow Royal Infirmary, Glasgow, UK

[e]Royal Infirmiary of Edinburgh, Edinburgh, UK

[f]The Freeman Hospital, Newcastle, UK

[g]Portsmouth NHS Hospitals Trust, Portsmouth, UK

[h]Patient representative, Coventry, UK

[i]University College London Hospitals NHS Foundation Trust, London, UK

[j]Warwick Medical School, University of Warwick, UK

[k]University of East Anglia, Norwich, UK

[l]Royal National Orthopaedic Hospital, Stanmore, UK

[m]Exeter Knee Reconstruction Unit, Princess Elizabeth Orthopaedic Centre, Exeter, UK

[n]Bristol Trials Centre, University of Bristol, UK

Corresponding authors (joint Chief Investigators):

Andrew J Metcalfe, Warwick Clinical Trials Unit, Warwick Medical School, University of Warwick, UK. Email: a.metcalfe@warwick.ac.uk

Edward T Davis, The Royal Orthopaedic Hospital NHS Foundation Trust, Birmingham, UK. Email: edward.davis@nhs.net

Word count (excluding title page, abstract, references and tables): 4349

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. 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 (RACER-Knee) is a multi-centre, participant-assessor blinded, randomised controlled trial to evaluate the clinical and cost-effectiveness of robotic-assisted TKR compared to 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 post-randomisation. 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, 29/07/20. NRES number: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

ISRCTN Number: 27624068

Article Summary

Strengths and limitations of this study

- Large, multicentre, randomised controlled trial of robotic-assisted total knee arthroplasty compared to 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 to analyses.

Keywords

Orthopaedic Surgery, Randomised Controlled Trials, Total Knee Replacement, Robotic Surgical Procedures, MAKO, Cost-effectiveness.

Introduction

Robotic-assisted knee replacements are increasingly common worldwide, with little high-quality evidence as to whether they are clinically or cost effective. (1) 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. (2) Whilst 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. (3-9)

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 computerised tomography (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 multi-factorial. It is proposed that some of these factors could be improved with better surgical technique and precision. (10-16) Robotic-assisted cuts may be more accurate and consistent. (17) 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 post-operative pain and facilitating earlier discharge. (18-20)

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. (21) 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. 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. (22) Another cost-effectiveness study showed

that robotic-arm assisted surgery could be cost-effective at a high volume for the health service. (23) 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 semi-active robotic-arm system available to the NHS (MAKO, Stryker, USA). Whilst other robotic-arm systems are becoming available, they are earlier in their development and clinical testing. (24) 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 RCTs using the MAKO system. (25) 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 to conventional instruments (N=40). These included reduced pain and earlier discharge. (18) A small randomised controlled trial showed reduced early post-operative inflammatory response. (26) This early reduction in post-inflammatory response was further confirmed by a small retrospective study. (27) 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 six months.(28) 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. (29) Bone cuts were more accurate with robotic surgery and there were non-significant differences, favouring robotic systems, in some clinical outcomes at one year. The potential benefits for TKR, a larger procedure involving more soft tissue exposure and with more heterogenous 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- 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 Forgotten Joint Score (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 three days after surgery, estimated blood loss, analgesic use, and time to discharge between groups.
- To compare the FJS, Oxford Knee Score (OKS), Oxford Activity & Participation Questionnaire (OAPQ), EQ-5D-5L, pain intensity, satisfaction, participant impression of change, adverse events, re-operation, and implant survival at three, six and 12 months and two, five- 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 randomised controlled trial to evaluate the clinical and cost-effectiveness of robotic-assisted TKR compared to conventional TKR in the UK healthcare setting. In the IDEAL classification, this represents a stage 3 study. (30)

Ethics and oversight

The trial received full ethical approval on 29th 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 and a Trial Steering Committee. Both groups will comprise of independent members in line with the relevant WCTU SOPs and 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.

Trial registration

The trial is registered with the ISRCTN register (Number:27624068). The current version of the protocol is V3.0 dated 26th November 2021.

Outcome measures

The choice of outcome measures was made in collaboration with our Patient and Public Involvement (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. (31) The FJS is a participant-reported outcome measure (PROM) 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. (32, 33) Twelve months will be the primary outcome timepoint as recovery after TKR has been demonstrated to plateau by this point and is maintained into the medium to long term. (34)

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 one, two and three after surgery. The NRS scale has been well-validated and widely used. (35, 36)
- Pain over the past 24 hours, when the operated knee is at rest and when it is moved, collected as above on the first three days.
- 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. (37)
- Opioid use to the end of day three as total morphine equivalent dose, using conversion methods established in a WCTU study on opioid reduction. (38)
- Hours from end of surgery to hospital discharge.

Participant reported outcomes

All collected at baseline (pre-randomisation); three, six, 12 months and two, five and 10 years post-randomisation.

- Overall knee function using the FJS.
- Health utility using EQ-5D-5L (additionally recorded at six weeks). (39, 40)
- Knee-related function using the OKS, a 12-item well-validated and widely used score. (41, 42)
- Higher level knee-related function using the OAPQ. (43)
- Pain over the last week using the three-item PROMIS Pain Intensity Scale (44)
- Satisfaction with the knee replacement using a five-point Likert scale (not at baseline). (45)
- The Participant Global Impression of Change, a single item, seven-point Likert scale question (not at baseline). (46)
- Re-operations and complications (not at baseline)
- Resource use using participant questionnaires (not at baseline)
- Resource use using NHS datasets (only at five and 10 years)

Safety outcomes

- Adverse events related to the operation, the anaesthetic, or the rehabilitation. Expected adverse events (including serious) will be recorded as outcomes. Serious adverse events will be collected according to relevant WCTU standard operating procedures.

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. (47)

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 contra-indicated (for example, 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; pre-operative 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 six months old will be collected again prior to randomisation.

Randomisation & treatment allocation

Randomisation will be done after the eligibility and consent review has taken place. Participants will be randomly allocated up to three 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, BMI (<35, ≥35) and primary compartment involved (medial, lateral or patellofemoral). (48)

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 re-registered 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 (TMG) and oversight committees.

Trial interventions

Group 1: Robotic total knee replacement (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 6.1mSv. This corresponds to 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.

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. All other care, including anaesthesia and post-operative analgesia, will be according to standard care.

Group 2: Conventional total knee replacement (control)

Participants allocated to the control group will receive TKR delivered using conventional instruments and the same Triathlon implants as the intervention group. The RACER-knee surgical manual will also describe the full details of the procedure. All implants will be cemented.

Two small incisions of 1cm 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 in-patient and out-patient physiotherapy has been developed for participants in both arms of the study. In accordance with 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. (49) 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. (49) The physiotherapy components will be reported in line with TIDieR and CERT criteria. (50, 51)

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 timepoint. At the request of the PPI group, participants will be informed of their treatment after they have completed the two-year 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 1cm 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. (52)

A customised operation note, based on previous experience in the START:REACTS study has been designed to ensure that intra-operative data collection regarding the robot is not a weak point in maintaining blinding. (53) 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 has 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

Patient and public involvement 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 co-investigator who is responsible for liaising with PPI co-investigators.

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 post-surgery.

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 adverse events (AEs), serious AEs (SAEs), serious adverse device events (SADEs) and unanticipated SADEs (USADEs) 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 post-randomisation 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 adverse events 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 post-randomisation will be collected. The co-sponsor (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 standard deviation (SD) of 30 points, resulting in a 20% difference in total score at 12 months and a moderate effect size of 0.4. (33, 54, 55). For power of 90% and a two-sided type I error rate of 5%, 266 participants are needed. After allowing for up to 20% loss to follow-up the required sample size is 332 participants.

Statistical analysis plan

All analyses will be reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines. (56) 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 (for example, 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 (≥35) and primary involved compartment (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. 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.

Pre-specified sub-group analyses will be undertaken to investigate whether the intervention effect differs between:

- BMI group (<35 or ≥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 a NHS and personal social services perspective, according to the recommendations of the NICE reference case. (57)

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 with 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, reflated to a common year. (58)

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 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. (59-61) 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.

Dissemination and Publication

The results of the trials will be reported in accordance with the CONSORT guidelines. (56) 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 de-identified 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 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.

Funding Statement

The RACER-knee study is funded by the NIHR Health Technology Assessment programme (reference number 12/87/68). The trial is co-sponsored by the University of Warwick and University Hospitals of Coventry and Warwickshire.

Author Contributions

All authors contributed to the development of the study protocol, assisting in the writing of the manuscript and approved the final version. JG led the writing and development of this paper. AM and ED are co-chief investigators and the main grant holders for this project and are responsible for identifying the clinical question. This paper and the study protocol were written following the SPIRIT guidelines for protocol development. A SPIRIT checklist has been included as a supporting document.(62)

Competing interests

Stryker is providing funding for consumables, pre-operative CT costs and 10 minutes of theatre time, according to contractual arrangements. They also fund some post-operative CT costs in the learning effects study. Appropriate contracts are in place to ensure the independence of the trial team with regards 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 Ltd., START:REACTS (16/61/18) (A Metcalfe, H Parsons, C Hutchinson, J Mason, M Underwood) and RACER-Hip (NIHR131407) (A Metcalfe, E Davis, H Parsons, S Rees, C Hutchinson, D Ellard, J Mason, F Haddad, J Skinner,M Underwood) . The full independence of the investigators of these related studies are protected by legal agreements, similar to this study. Mr FS Haddad receives funding from Stryker to run clinical studies.

Multiple authors report other unrelated research grants from NIHR during the conduct of the study.

D Ellard, H Parsons and J Griffin are supported from NIHR Research Capability Funding via University Hospitals Coventry and Warwickshire."

M Underwood is chief investigator or co-investigator on multiple previous and current research grants from the UK National Institute for Health Research, Arthritis Research UK and is a co-investigator 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 Clinvivo Ltd 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.

Disclaimer

Views expressed in the publication are representative of the authors and not necessarily those of the NIHR or the Department of Health and Social Care

Open access

References

1. AOANJRR. Australian Orthopaedic Association National Joint Replacement Registry (AOANJRR) Hip, Knee & Shoulder Arthroplasty: 2021 Annual Report. Adelaide, AOA: [Accessed from: https://aoanjrr.sahmri.com/annual-reports-2021]; 2021. p. 193
2. Commitee N. National Joint Registry for England, Wales, Northern Ireland and the Isle of Man: 15th annual report, 2017. National Joint Registry Centre. 2018.
3. Anderson JG, Wixson RL, Tsai D, Stulberg SD, Chang RW. Functional outcome and patient satisfaction in total knee patients over the age of 75. The Journal of arthroplasty. 1996;11(7):831-40.
4. Bourne RB, Chesworth BM, Davis AM, Mahomed NN, Charron KD. Patient satisfaction after total knee arthroplasty: who is satisfied and who is not? Clinical Orthopaedics and Related Research®. 2010;468(1):57-63.
5. Hawker G, Wright J, Coyte P, Paul J, Dittus R, Croxford R, et al. Health-related quality of life after knee replacement. Results of the knee replacement patient outcomes research team study. Jbjs. 1998;80(2):163-73.
6. Kahlenberg CA, Nwachukwu BU, McLawhorn AS, Cross MB, Cornell CN, Padgett DE. Patient satisfaction after total knee replacement: a systematic review. HSS Journal®. 2018;14(2):192-201.
7. Robertsson O, Dunbar M, Pehrsson T, Knutson K, Lidgren L. Patient satisfaction after knee arthroplasty: a report on 27,372 knees operated on between 1981 and 1995 in Sweden. Acta Orthopaedica Scandinavica. 2000;71(3):262-7.
8. Skou ST, Roos EM, Laursen MB, Rathleff MS, Arendt-Nielsen L, Simonsen O, et al. A Randomized, Controlled Trial of Total Knee Replacement. New England Journal of Medicine. 2015;373(17):1597-606.
9. Beswick AD, Wylde V, Gooberman-Hill R, Blom A, Dieppe P. What proportion of patients report long-term pain after total hip or knee replacement for osteoarthritis? A systematic review of prospective studies in unselected patients. BMJ open. 2012;2(1):e000435.
10. Wylde V, Dieppe P, Hewlett S, Learmonth ID. Total knee replacement: is it really an effective procedure for all? The Knee. 2007;14:417-23.
11. Kim DH, Pearson-Chauhan KM, McCarthy RJ, Buvanendran A. Predictive Factors for Developing Chronic Pain After Total Knee Arthroplasty. J Arthroplasty. 2018;33(11):3372-8.
12. Bell SW, Young P, Drury C, Smith J, Anthony I, Jones B, et al. Component rotational alignment in unexplained painful primary total knee arthroplasty. Knee. 2014;21(1):272-7.
13. Panni AS, Ascione F, Rossini M, Braile A, Corona K, Vasso M, et al. Tibial internal rotation negatively affects clinical outcomes in total knee arthroplasty: a systematic review. Knee Surg Sports Traumatol Arthrosc. 2018;26(6):1636-44.
14. Kim JH. Effect of posterior femoral condylar offset and posterior tibial slope on maximal flexion angle of the knee in posterior cruciate ligament sacrificing total knee arthroplasty. Knee Surg Relat Res. 2013;25(2):54-9.
15. Kemp MA, Metcalfe AJ, Sayers A, Wylde V, Eldridge JD, Blom AW. Does overstuffing of the patellofemoral joint in total knee arthroplasty have a significant effect on postoperative outcomes? Knee. 2018;25(5):874-81.
16. Kazarian GS, Lieberman EG, Hansen EJ, Nunley RM, Barrack RL. Clinical impact of component placement in manually instrumented total knee arthroplasty: a systematic review. The bone & joint journal. 2021;103(9):1449-56.
17. Zhang J, Ndou WS, Ng N, Gaston P, Simpson PM, Macpherson GJ, et al. Robotic-arm assisted total knee arthroplasty is associated with improved accuracy and patient reported outcomes: a systematic review and meta-analysis. Knee Surgery, Sports Traumatology, Arthroscopy. 2021:1-19.
18. Kayani B, Konan S, Tahmassebi J, Pietrzak JRT, Haddad FS. Robotic-arm assisted total knee arthroplasty is associated with improved early functional recovery and reduced time to hospital discharge compared with conventional jig-based total knee arthroplasty: a prospective cohort study. Bone Joint J. 2018;100-b(7):930-7.

19. Kayani B, Konan S, Pietrzak JR, Haddad FS. Iatrogenic bone and soft tissue trauma in robotic-arm assisted total knee arthroplasty compared with conventional jig-based total knee arthroplasty: a prospective cohort study and validation of a new classification system. The Journal of arthroplasty. 2018;33(8):2496-501.
20. Khlopas A, Chughtai M, Hampp EL, Scholl LY, Prieto M, Chang T-C, et al. Robotic-Arm Assisted Total Knee Arthroplasty Demonstrated Soft Tissue Protection. Surgical technology international. 2017;30:441-6.
21. Baek J-H, Lee SC, Kim J-H, Ahn HS, Nam CH. Distal Femoral Pin Tracker Placement Prevents Pin Tract-induced Fracture in Robotic-Assisted Total Knee Arthroplasty. The Journal of Knee Surgery. 2021.
22. Cool CL, Jacofsky DJ, Seeger KA, Sodhi N, Mont MA. A 90-day episode-of-care cost analysis of robotic-arm assisted total knee arthroplasty. Journal of Comparative Effectiveness Research. 2019;8(5):327-36.
23. Vermue H, Tack P, Gryson T, Victor J. Can robot-assisted total knee arthroplasty be a cost-effective procedure? A Markov decision analysis. The Knee. 2021;29:345-52.
24. Chen AF, Kazarian GS, Jessop GW, Makhdom A. Robotic Technology in Orthopaedic Surgery. J Bone Joint Surg Am. 2018;100(22):1984-92.
25. Agarwal N, To K, McDonnell S, Khan W. Clinical and radiological outcomes in robotic-assisted total knee arthroplasty: a systematic review and meta-analysis. The Journal of arthroplasty. 2020.
26. Kayani B, Tahmassebi J, Ayuob A, Konan S, Oussedik S, Haddad FS. A prospective randomized controlled trial comparing the systemic inflammatory response in conventional jig-based total knee arthroplasty versus robotic-arm assisted total knee arthroplasty. Bone Joint J. 2021;103-b(1):113-22.
27. Xu JZ, Li LL, Fu J, Xu C, Zhang GQ, Chai W, et al. Comparison of serum inflammatory indicators and radiographic results in MAKO robotic-assisted versus conventional total knee arthroplasty for knee osteoarthritis: a retrospective study of Chinese patients. BMC Musculoskelet Disord. 2022;23(1):418.
28. Marchand RC, Sodhi N, Khlopas A, Sultan AA, Harwin SF, Malkani AL, et al. Patient Satisfaction Outcomes after Robotic Arm-Assisted Total Knee Arthroplasty: A Short-Term Evaluation. J Knee Surg. 2017;30(9):849-53.
29. Gilmour A, MacLean AD, Rowe PJ, Banger MS, Donnelly I, Jones BG, et al. Robotic-Arm-Assisted vs Conventional Unicompartmental Knee Arthroplasty. The 2-Year Clinical Outcomes of a Randomized Controlled Trial. J Arthroplasty. 2018;33(7S):S109-S15.
30. McCulloch P, Altman DG, Campbell WB, Flum DR, Glasziou P, Marshall JC, et al. No surgical innovation without evaluation: the IDEAL recommendations. Lancet. 2009;374(9695):1105-12.
31. Behrend H, Giesinger K, Giesinger JM, Kuster MS. The “forgotten joint” as the ultimate goal in joint arthroplasty: validation of a new patient-reported outcome measure. The Journal of arthroplasty. 2012;27(3):430-6. e1.
32. Hamilton DF, Loth FL, Giesinger JM, Giesinger K, MacDonald DJ, Patton JT, et al. Validation of the English language Forgotten Joint Score-12 as an outcome measure for total hip and knee arthroplasty in a British population. Bone Joint J. 2017;99-b(2):218-24.
33. Thomsen MG, Latifi R, Kallemose T, Barfod KW, Husted H, Troelsen A. Good validity and reliability of the forgotten joint score in evaluating the outcome of total knee arthroplasty. Acta Orthop. 2016;87(3):280-5.
34. Carlson VR, Post ZD, Orozco FR, Davis DM, Lutz RW, Ong AC. When does the knee feel normal again: a cross-sectional study assessing the forgotten joint score in patients after total knee arthroplasty. The Journal of arthroplasty. 2018;33(3):700-3.
35. Williamson A, Hoggart B. Pain: a review of three commonly used pain rating scales. J Clin Nurs. 2005;14(7):798-804.
36. Wall PDH, Parsons H, Achten J, Balasubramanian S, Thompson P, Costa ML, et al. A pragmatic randomised controlled trial comparing the efficacy of a femoral nerve block and periarticular infiltration for early pain relief following total knee arthroplasty. Bone and Joint Journal. 2017;99-B:904-11.

37. Brecher ME, Monk T, Goodnough LT. A standardized method for calculating blood loss. Transfusion. 1997;37(10):1070-4.
38. Sandhu HK, Abraham C, Alleyne S, Balasubramanian S, Betteley L, Booth K, et al. Testing a support programme for opioid reduction for people with chronic non-malignant pain: the I-WOTCH randomised controlled trial protocol. BMJ Open. 2019;9(8):e028937.
39. EuroQol G. EuroQol--a new facility for the measurement of health-related quality of life. Health Policy. 1990;16(3):199-208.
40. Fransen M, Edmonds J. Reliability and validity of the EuroQol in patients with osteoarthritis of the knee. 1999:807-13.
41. Beard DJ, Harris K, Dawson J, Doll H, Murray DW, Carr AJ, et al. Meaningful changes for the Oxford hip and knee scores after joint replacement surgery. Journal of clinical epidemiology. 2015;68:73-9.
42. Dawson J, Fitzpatrick R, Murray D, Carr A. Questionnaire on the perceptions of patients about total knee replacement. Journal of Bone and Joint Surgery (British Edition). 1998;80:63-9.
43. Dawson J, Beard DJ, McKibbin H, Harris K, Jenkinson C, Price aJ. Development of a patient-reported outcome measure of activity and participation (the OKSAPQ) to supplement the Oxford knee score. Bone and Joint Journal. 2014;96 B:332-8.
44. Stone AA, Broderick JE, Junghaenel DU, Schneider S, Schwartz JE. PROMIS fatigue, pain intensity, pain interference, pain behavior, physical function, depression, anxiety, and anger scales demonstrate ecological validity. J Clin Epidemiol. 2016;74:194-206.
45. Rolfson O, Bohm E, Franklin P, Lyman S, Denissen G, Dawson J, et al. Patient-reported outcome measures in arthroplasty registries Report of the Patient-Reported Outcome Measures Working Group of the International Society of Arthroplasty Registries Part II. Recommendations for selection, administration, and analysis. Acta Orthop. 2016;87 Suppl 1:9-23.
46. Kamper SJ, Maher CG, Mackay G. Global rating of change scales: a review of strengths and weaknesses and considerations for design. J Man Manip Ther. 2009;17(3):163-70.
47. National Clinical Guideline C. National Institute for Health and Clinical Excellence: Guidance. Osteoarthritis: Care and Management in Adults. London: National Institute for Health and Care Excellence (UK)

48. Altman DG, Bland JM. Treatment allocation by minimisation. Bmj. 2005;330(7495):843.
49. NICE. Joint replacement (primary): hip, knee and shoulder [NG157]. London, UK: NICE; 2020.
50. Hoffmann TC, Glasziou PP, Boutron I, Milne R, Perera R, Moher D, et al. Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. Bmj. 2014;348:g1687.
51. Slade SC, Dionne CE, Underwood M, Buchbinder R. Consensus on Exercise Reporting Template (CERT): Explanation and Elaboration Statement. Br J Sports Med. 2016;50(23):1428-37.
52. George AJT, Collett C, Carr AJ, Holm S, Bale C, Burton S, et al. When should placebo surgery as a control in clinical trials be carried out? The Bulletin of the Royal College of Surgeons of England. 2016;98(2):75-9.
53. Metcalfe A, Parsons H, Parsons N, Brown J, Fox J, Mannion EG, et al. Subacromial balloon spacer for irreparable rotator cuff tears of the shoulder (START: REACTS): a group-sequential, double-blind, multicentre randomised controlled trial. The Lancet. 2022;399(10339):1954-63.
54. Thompson SM, Salmon LJ, Webb JM, Pinczewski LA, Roe JP. Construct validity and test re-test reliability of the forgotten joint score. The Journal of arthroplasty. 2015;30(11):1902-5.

55. Clement ND, Scott CE, Hamilton DF, MacDonald D, Howie CR. Meaningful values in the Forgotten Joint Score after total knee arthroplasty. The Bone & Joint Journal. 2021;103(5):846-54.
56. Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. Bmj. 2010;340:c332.
57. NICE U. Guide to the methods of technology appraisal. National Institute for Health and Clinical Excellence (NICE) London, UK. 2013.
58. Curtis LA, Burns A. Unit costs of health and social care 2015: Personal Social Services Research Unit; 2015.
59. Manca A, Hawkins N, Sculpher MJ. Estimating mean QALYs in trial-based cost-effectiveness analysis: the importance of controlling for baseline utility. Health economics. 2005;14(5):487-96.
60. Sterne JA, White IR, Carlin JB, Spratt M, Royston P, Kenward MG, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. Bmj. 2009;338.
61. White IR, Horton NJ, Carpenter J, Pocock SJ. Strategy for intention to treat analysis in randomised trials with missing outcome data. Bmj. 2011;342.
62. Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin JA, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. Bmj. 2013;346.

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1,4
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	5
	2b	All items from the World Health Organization Trial Registration Data Set	-
Protocol version	3	Date and version identifier	5
Funding	4	Sources and types of financial, material, and other support	13
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	13
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	13
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	5

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3-4
	6b	Explanation for choice of comparators	3-4
Objectives	7	Specific objectives or hypotheses	4
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	4,7
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	9
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8-9
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10-11
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	10
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	11
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	-
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7-8
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	7

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	14	
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	10	
Methods: Assignment of interventions (for controlled trials)				
Allocation:				
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	10	
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	10	
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	10	
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	11	
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	12	
Methods: Data collection, management, and analysis				
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol		7-8
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	7-8	

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	8
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	14
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	14
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	14
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	7
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	-
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	13
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	-
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	3
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	-

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	9
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	-
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	8
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	17
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	-
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	-
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	16
	31b	Authorship eligibility guidelines and any intended use of professional writers	-
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	-
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	-
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	-

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-068255.R1
Article Type:	Protocol
Date Submitted by the Author:	26-Jan-2023

Complete List of Authors:	Griffin, James; University of Warwick Warwick Clinical Trials Unit, Warwick Medical School; University Hospitals Coventry and Warwickshire NHS Trust Davis, ET; Royal Orthopaedic Hospital NHS Foundation Trust Parsons, Helen; University of Warwick Warwick Clinical Trials Unit, Warwick Medical School; University Hospitals Coventry and Warwickshire NHS Trust Gemperle Mannion, Elke; University of Warwick Warwick Clinical Trials Unit, Warwick Medical School Khatri, Chetan; University of Warwick Warwick Clinical Trials Unit, Clinical Trials Unit; University Hospitals Coventry and Warwickshire NHS Trust Ellard, David; University of Warwick Warwick Clinical Trials Unit, Warwick Medical School; University Hospitals Coventry and Warwickshire NHS Trust, Blyth, MJ; Glasgow Royal Infirmary, Orthopaedic Research Unit, Department of Trauma and Orthopaedics Clement, Nicholas; Royal Infirmary of Edinburgh, Orthopaedics and Trauma; University of Edinburgh Division of Clinical and Surgical Sciences, Orthopaedics Deehan, David; Newcastle Upon Tyne Hospitals NHS Trust Flynn, Nicholas; Portsmouth Hospitals NHS Trust Fox, Josephine; Patient Representative Grant, Nicholas; Patient Representative Haddad, Fares; University College London Hospitals NHS Foundation Trust Hutchinson, Charles; University of Warwick Warwick Medical School, Warwick Medical School; University Hospitals Coventry and Warwickshire NHS Trust Mason, James; University of Warwick Warwick Clinical Trials Unit, Warwick Medical School Mohindru, Bishal; University of Warwick Warwick Clinical Trials Unit Scott, Chloe; Royal Infirmary of Edinburgh, Orthopaedics; University of Edinburgh Division of Clinical and Surgical Sciences, Smith, Toby; University of East Anglia, Faculty of Medicine and Health Sciences; University of Oxford, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences Skinner, John; Royal National Orthopaedic Hospital NHS Trust Toms, Andrew ; Royal Devon and Exeter NHS Foundation Trust Rees, Sophie; University of Bristol, Bristol Trials Centre Underwood, Martin; University of Warwick Warwick Clinical Trials Unit,

	Warwick Medical School; University Hospitals Coventry and Warwickshire NHS Trust Metcalfe, Andrew; University of Warwick Warwick Clinical Trials Unit; University Hospitals Coventry and Warwickshire NHS Trust
Primary Subject Heading:	Surgery
Secondary Subject Heading:	Rehabilitation medicine
Keywords:	ORTHOPAEDIC & TRAUMA SURGERY, Knee < ORTHOPAEDIC & TRAUMA SURGERY, Adult orthopaedics < ORTHOPAEDIC & TRAUMA SURGERY, Adult surgery < SURGERY

The Robotic Arthroplasty Clinical and cost Effectiveness Randomised controlled trial (RACER-knee): a study protocol.

Mr J Griffin[a,c], Professor ET Davis[b], Dr H Parsons[a,c], Mrs E Gemperle Mannion[a], Mr C Khatri[a,c], Professor DR Ellard[a,c], Mr MJ Blyth[d], Mr ND Clement[e], Mr D Deehan[f], Mr N Flynn[g], Miss J Fox[h], Mr NJ Grant[h], Mr FS Haddad[i], Professor CE Hutchinson[c,j], Professor J Mason[a], Dr B Mohindru[a], Ms CEH Scott[e], Dr TO Smith[a], Professor JA Skinner[k], Professor AD Toms[l], Dr S Rees[m], Professor M Underwood[a,c], Mr AJ Metcalfe[a,c]

[a]Warwick Clinical Trials Unit, Warwick Medical School, University of Warwick, UK.

[b]The Royal Orthopaedic Hospital NHS Foundation Trust, Birmingham, UK.

[c]University Hospitals Coventry and Warwickshire NHS Trust, Coventry, UK

[d]Glasgow Royal Infirmary, Glasgow, UK

[e]Royal Infirmiary of Edinburgh, Edinburgh, UK

[f]The Freeman Hospital, Newcastle, UK

[g]Portsmouth NHS Hospitals Trust, Portsmouth, UK

[h]Patient representative, Coventry, UK

[i]University College London Hospitals NHS Foundation Trust, London, UK

[j]Warwick Medical School, University of Warwick, UK

[k]Royal National Orthopaedic Hospital, Stanmore, UK

[l]Exeter Knee Reconstruction Unit, Princess Elizabeth Orthopaedic Centre, Exeter, UK

[m]Bristol Trials Centre, University of Bristol, UK

Corresponding author:

James Griffin, Warwick Clinical Trials Unit, Warwick Medical School, University of Warwick, UK. Email: james.griffin@warwick.ac.uk

Word count (excluding title page, abstract, references and tables): 4508

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 (RACER-Knee) is a multi-centre, participant-assessor blinded, randomised controlled trial to evaluate the clinical and cost-effectiveness of robotic-assisted TKR compared to 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 post-randomisation. 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, 29/07/20. NRES number: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

ISRCTN Number: 27624068

Article Summary

Strengths and limitations of this study

- Large, multicentre, randomised controlled trial of robotic-assisted total knee arthroplasty compared to 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.

Keywords

Orthopaedic Surgery, Randomised Controlled Trials, Total Knee Replacement, Robotic Surgical Procedures, MAKO, Cost-effectiveness.

Introduction

Robotic-assisted knee replacements are increasingly common worldwide, with little high-quality evidence as to whether they are clinically or cost effective. (1) 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. (2) Whilst 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. (3, 4, 5, 6, 7, 8, 9)

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 computerised tomography (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 multi-factorial. It is proposed that some of these factors could be improved with better surgical technique and precision. (10, 11, 12, 13, 14, 15, 16) Robotic-assisted cuts may be more accurate and consistent. (17) 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 post-operative pain and facilitating earlier discharge. (18, 19, 20)

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. (21) 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. (22) Another cost-effectiveness study showed that robotic-arm assisted surgery could be cost-effective at a high volume for the health service. (23) 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 semi-active robotic-arm system available to the NHS (MAKO, Stryker, USA). Whilst other robotic-arm systems are becoming available, they are earlier in their development and clinical testing. (24) 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 RCTs using the MAKO system. (25) 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 to conventional instruments (N=40). These included reduced pain and earlier discharge. (18) A small randomised controlled trial showed reduced early post-operative inflammatory response. (26) This early reduction in post-inflammatory response was further confirmed by a small retrospective study. (27) 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 six months.(28) 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. (29) Bone cuts were more accurate with robotic surgery and whilst clinical outcomes (including the Forgotten Joint Score and the Oxford Knee Score) were similar at two years, there were non-significant differences favouring robotic systems in some clinical

outcomes (including early pain and the Forgotten Joint Score) at one year. (29) The potential benefits for TKR, a larger procedure involving more soft tissue exposure and with more heterogenous 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- 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 Forgotten Joint Score (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 three days after surgery, estimated blood loss, analgesic use, and time to discharge between groups.
- To compare the FJS, Oxford Knee Score (OKS), Oxford Activity & Participation Questionnaire (OAPQ), EQ-5D-5L, pain intensity, satisfaction, participant impression of change, adverse events, re-operation, and implant survival at three, six and 12 months and two, five- 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 randomised controlled trial to evaluate the clinical and cost-effectiveness of robotic-assisted TKR compared to conventional TKR in the UK healthcare setting. In the IDEAL classification, this represents a stage 3 study. (30)

Ethics and Dissemination

The trial received full ethical approval on 29th 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 and a Trial Steering Committee. Both groups will comprise of independent members in line with the relevant WCTU SOPs and 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 CONSORT guidelines. (31) 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 de-identified 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 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 26th 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 Patient and Public Involvement (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. (32) The FJS is a participant-reported outcome measure (PROM) 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. (33, 34) Twelve months will be the primary outcome timepoint as recovery after TKR has been demonstrated to plateau by this point and is maintained into the medium to long term. (35)

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 one, two and three after surgery. The NRS scale has been well-validated and widely used. (36, 37)
- Pain over the past 24 hours, when the operated knee is at rest and when it is moved, collected as above on the first three days.
- 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. (38)
- Opioid use to the end of day three as total morphine equivalent dose, using conversion methods established in a WCTU study on opioid reduction. (39)
- Hours from end of surgery to hospital discharge.

Participant reported outcomes

All collected at baseline (pre-randomisation); three, six, 12 months and two, five and 10 years post-randomisation.

- Overall knee function using the FJS.
- Health utility using EQ-5D-5L (additionally recorded at six weeks). (40, 41)
- Knee-related function using the OKS, a 12-item well-validated and widely used score. (42, 43)
- Higher level knee-related function using the OAPQ. (44)
- Pain over the last week using the three-item PROMIS Pain Intensity Scale (45)
- Satisfaction with the knee replacement using a five-point Likert scale (not at baseline). (46)
- The Participant Global Impression of Change, a single item, seven-point Likert scale question (not at baseline). (47)
- Re-operations and complications (not at baseline), categorised into revision procedures using the National Joint Registry definition, and other re-operations. (2)
- Resource use using participant questionnaires (not at baseline)

- Resource use using NHS datasets (only at five and 10 years)

Safety outcomes

- Adverse events related to the operation, the anaesthetic, or the rehabilitation. Expected adverse events (including serious) will be recorded as outcomes. Serious adverse events will be collected according to relevant WCTU standard operating procedures.

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. (48)

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 contra-indicated (for example, 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; pre-operative 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 six months old will be collected again prior to randomisation.

Randomisation & treatment allocation

Randomisation will be done after the eligibility and consent review has taken place. Participants will be randomly allocated up to three 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, BMI (<35, ≥35) and primary compartment involved (medial, lateral or patellofemoral). (49)

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 re-registered 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 (TMG) and oversight committees.

Trial interventions

Group 1: Robotic total knee replacement (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 6.1mSv. This corresponds to 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.

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. Whilst 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 post-operative analgesia, will be according to standard care.

Group 2: Conventional total knee replacement (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, whilst 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 1cm 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 in-patient and out-patient physiotherapy has been developed for participants in both arms of the study. In accordance with 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. (50) 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. (50) The physiotherapy components will be reported in line with TIDieR and CERT criteria. (51, 52)

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 timepoint. At the request of the PPI group, participants will be informed of their treatment after they have completed the two-year 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 1cm 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. (53)

A customised operation note, based on previous experience in the START:REACTS study has been designed to ensure that intra-operative data collection regarding the robot is not a weak point in maintaining blinding. (54) 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 has 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

Patient and public involvement 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 co-investigator who is responsible for liaising with PPI co-investigators.

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 post-surgery.

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 adverse events (AEs), serious AEs (SAEs), serious adverse device events (SADEs) and unanticipated SADEs (USADEs) 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 post-randomisation 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 adverse events 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 post-randomisation will be collected. The co-sponsor (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 standard deviation (SD) of 30 points based on estimates taken from two population-based studies. (34, 55, 56). 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% loss to follow-up the required sample size is 332 participants.

Statistical analysis plan

All analyses will be reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines. (31) 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 (for example, 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 (≥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 re-operation 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.

Pre-specified sub-group analyses will be undertaken to investigate whether the intervention effect differs between:

- BMI group (<35 or ≥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 a NHS and personal social services perspective, according to the recommendations of the NICE reference case. (57)

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 with 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, reflated to a common year. (58)

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 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. (59, 60, 61) 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.

Funding Statement

The RACER-knee study is funded by the NIHR Health Technology Assessment programme (reference number 12/87/68). The trial is co-sponsored by the University of Warwick and University Hospitals of Coventry and Warwickshire.

Author Contributions

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.

Competing interests

Stryker is providing funding for consumables, pre-operative CT costs and 10 minutes of theatre time, according to contractual arrangements. They also fund some post-operative CT costs in the learning effects study. Appropriate contracts are in place to ensure the independence of the trial team with regards 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 Ltd., START:REACTS (16/61/18) (A Metcalfe, H Parsons, C Hutchinson, J

Mason, M Underwood) and RACER-Hip (NIHR131407) (A Metcalfe, E Davis, H Parsons, S Rees, C Hutchinson, D Ellard, J Mason, F Haddad, J Skinner,M Underwood) . The full independence of the investigators of these related studies are protected by legal agreements, similar to this study. Mr FS Haddad receives funding from Stryker to run clinical studies.

Multiple authors report other unrelated research grants from NIHR during the conduct of the study.

D Ellard, H Parsons and J Griffin are supported from NIHR Research Capability Funding via University Hospitals Coventry and Warwickshire."

M Underwood is chief investigator or co-investigator on multiple previous and current research grants from the UK National Institute for Health Research, Arthritis Research UK and is a co-investigator 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 Clinvivo Ltd 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.

Disclaimer

Views expressed in the publication are representative of the authors and not necessarily those of the NIHR or the Department of Health and Social Care

Open access

References

1. AOANJRR. Australian Orthopaedic Association National Joint Replacement Registry (AOANJRR) Hip, Knee & Shoulder Arthroplasty: 2021 Annual Report. Adelaide, AOA: [Accessed from: https://aoanjrr.sahmri.com/annual-reports-2021]; 2021. p. 193
2. Commitee N. National Joint Registry for England, Wales, Northern Ireland and the Isle of Man: 15th annual report, 2017. National Joint Registry Centre. 2018.
3. Anderson JG, Wixson RL, Tsai D, Stulberg SD, Chang RW. Functional outcome and patient satisfaction in total knee patients over the age of 75. The Journal of arthroplasty. 1996;11(7):831-40.
4. Bourne RB, Chesworth BM, Davis AM, Mahomed NN, Charron KD. Patient satisfaction after total knee arthroplasty: who is satisfied and who is not? Clinical Orthopaedics and Related Research®. 2010;468(1):57-63.
5. Hawker G, Wright J, Coyte P, Paul J, Dittus R, Croxford R, et al. Health-related quality of life after knee replacement. Results of the knee replacement patient outcomes research team study. Jbjs. 1998;80(2):163-73.
6. Kahlenberg CA, Nwachukwu BU, McLawhorn AS, Cross MB, Cornell CN, Padgett DE. Patient satisfaction after total knee replacement: a systematic review. HSS Journal®. 2018;14(2):192-201.
7. Robertsson O, Dunbar M, Pehrsson T, Knutson K, Lidgren L. Patient satisfaction after knee arthroplasty: a report on 27,372 knees operated on between 1981 and 1995 in Sweden. Acta Orthopaedica Scandinavica. 2000;71(3):262-7.
8. Skou ST, Roos EM, Laursen MB, Rathleff MS, Arendt-Nielsen L, Simonsen O, et al. A Randomized, Controlled Trial of Total Knee Replacement. New England Journal of Medicine. 2015;373(17):1597-606.
9. Beswick AD, Wylde V, Gooberman-Hill R, Blom A, Dieppe P. What proportion of patients report long-term pain after total hip or knee replacement for osteoarthritis? A systematic review of prospective studies in unselected patients. BMJ open. 2012;2(1):e000435.
10. Wylde V, Dieppe P, Hewlett S, Learmonth ID. Total knee replacement: is it really an effective procedure for all? The Knee. 2007;14:417-23.
11. Kim DH, Pearson-Chauhan KM, McCarthy RJ, Buvanendran A. Predictive Factors for Developing Chronic Pain After Total Knee Arthroplasty. J Arthroplasty. 2018;33(11):3372-8.
12. Bell SW, Young P, Drury C, Smith J, Anthony I, Jones B, et al. Component rotational alignment in unexplained painful primary total knee arthroplasty. Knee. 2014;21(1):272-7.
13. Panni AS, Ascione F, Rossini M, Braile A, Corona K, Vasso M, et al. Tibial internal rotation negatively affects clinical outcomes in total knee arthroplasty: a systematic review. Knee Surg Sports Traumatol Arthrosc. 2018;26(6):1636-44.
14. Kim JH. Effect of posterior femoral condylar offset and posterior tibial slope on maximal flexion angle of the knee in posterior cruciate ligament sacrificing total knee arthroplasty. Knee Surg Relat Res. 2013;25(2):54-9.
15. Kemp MA, Metcalfe AJ, Sayers A, Wylde V, Eldridge JD, Blom AW. Does overstuffing of the patellofemoral joint in total knee arthroplasty have a significant effect on postoperative outcomes? Knee. 2018;25(5):874-81.
16. Kazarian GS, Lieberman EG, Hansen EJ, Nunley RM, Barrack RL. Clinical impact of component placement in manually instrumented total knee arthroplasty: a systematic review. The bone & joint journal. 2021;103(9):1449-56.
17. Zhang J, Ndou WS, Ng N, Gaston P, Simpson PM, Macpherson GJ, et al. Robotic-arm assisted total knee arthroplasty is associated with improved accuracy and patient reported outcomes: a systematic review and meta-analysis. Knee Surgery, Sports Traumatology, Arthroscopy. 2021:1-19.
18. Kayani B, Konan S, Tahmassebi J, Pietrzak JRT, Haddad FS. Robotic-arm assisted total knee arthroplasty is associated with improved early functional recovery and reduced time to hospital discharge compared with conventional jig-based total knee arthroplasty: a prospective cohort study. Bone Joint J. 2018;100-b(7):930-7.

19. Kayani B, Konan S, Pietrzak JR, Haddad FS. Iatrogenic bone and soft tissue trauma in robotic-arm assisted total knee arthroplasty compared with conventional jig-based total knee arthroplasty: a prospective cohort study and validation of a new classification system. The Journal of arthroplasty. 2018;33(8):2496-501.
20. Khlopas A, Chughtai M, Hampp EL, Scholl LY, Prieto M, Chang T-C, et al. Robotic-Arm Assisted Total Knee Arthroplasty Demonstrated Soft Tissue Protection. Surgical technology international. 2017;30:441-6.
21. Baek J-H, Lee SC, Kim J-H, Ahn HS, Nam CH. Distal Femoral Pin Tracker Placement Prevents Pin Tract-induced Fracture in Robotic-Assisted Total Knee Arthroplasty. The Journal of Knee Surgery. 2021.
22. Cool CL, Jacofsky DJ, Seeger KA, Sodhi N, Mont MA. A 90-day episode-of-care cost analysis of robotic-arm assisted total knee arthroplasty. Journal of Comparative Effectiveness Research. 2019;8(5):327-36.
23. Vermue H, Tack P, Gryson T, Victor J. Can robot-assisted total knee arthroplasty be a cost-effective procedure? A Markov decision analysis. The Knee. 2021;29:345-52.
24. Chen AF, Kazarian GS, Jessop GW, Makhdom A. Robotic Technology in Orthopaedic Surgery. J Bone Joint Surg Am. 2018;100(22):1984-92.
25. Agarwal N, To K, McDonnell S, Khan W. Clinical and radiological outcomes in robotic-assisted total knee arthroplasty: a systematic review and meta-analysis. The Journal of arthroplasty. 2020.
26. Kayani B, Tahmassebi J, Ayuob A, Konan S, Oussedik S, Haddad FS. A prospective randomized controlled trial comparing the systemic inflammatory response in conventional jig-based total knee arthroplasty versus robotic-arm assisted total knee arthroplasty. Bone Joint J. 2021;103-b(1):113-22.
27. Xu JZ, Li LL, Fu J, Xu C, Zhang GQ, Chai W, et al. Comparison of serum inflammatory indicators and radiographic results in MAKO robotic-assisted versus conventional total knee arthroplasty for knee osteoarthritis: a retrospective study of Chinese patients. BMC Musculoskelet Disord. 2022;23(1):418.
28. Marchand RC, Sodhi N, Khlopas A, Sultan AA, Harwin SF, Malkani AL, et al. Patient Satisfaction Outcomes after Robotic Arm-Assisted Total Knee Arthroplasty: A Short-Term Evaluation. J Knee Surg. 2017;30(9):849-53.
29. Gilmour A, MacLean AD, Rowe PJ, Banger MS, Donnelly I, Jones BG, et al. Robotic-Arm-Assisted vs Conventional Unicompartmental Knee Arthroplasty. The 2-Year Clinical Outcomes of a Randomized Controlled Trial. J Arthroplasty. 2018;33(7S):S109-S15.
30. McCulloch P, Altman DG, Campbell WB, Flum DR, Glasziou P, Marshall JC, et al. No surgical innovation without evaluation: the IDEAL recommendations. Lancet. 2009;374(9695):1105-12.
31. Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. Bmj. 2010;340:c332.
32. Behrend H, Giesinger K, Giesinger JM, Kuster MS. The “forgotten joint” as the ultimate goal in joint arthroplasty: validation of a new patient-reported outcome measure. The Journal of arthroplasty. 2012;27(3):430-6. e1.
33. Hamilton DF, Loth FL, Giesinger JM, Giesinger K, MacDonald DJ, Patton JT, et al. Validation of the English language Forgotten Joint Score-12 as an outcome measure for total hip and knee arthroplasty in a British population. Bone Joint J. 2017;99-b(2):218-24.
34. Thomsen MG, Latifi R, Kallemose T, Barfod KW, Husted H, Troelsen A. Good validity and reliability of the forgotten joint score in evaluating the outcome of total knee arthroplasty. Acta Orthop. 2016;87(3):280-5.
35. Carlson VR, Post ZD, Orozco FR, Davis DM, Lutz RW, Ong AC. When does the knee feel normal again: a cross-sectional study assessing the forgotten joint score in patients after total knee arthroplasty. The Journal of arthroplasty. 2018;33(3):700-3.
36. Williamson A, Hoggart B. Pain: a review of three commonly used pain rating scales. J Clin Nurs. 2005;14(7):798-804.

37. Wall PDH, Parsons H, Achten J, Balasubramanian S, Thompson P, Costa ML, et al. A pragmatic randomised controlled trial comparing the efficacy of a femoral nerve block and periarticular infiltration for early pain relief following total knee arthroplasty. Bone and Joint Journal. 2017;99-B:904-11.
38. Brecher ME, Monk T, Goodnough LT. A standardized method for calculating blood loss. Transfusion. 1997;37(10):1070-4.
39. Sandhu HK, Abraham C, Alleyne S, Balasubramanian S, Betteley L, Booth K, et al. Testing a support programme for opioid reduction for people with chronic non-malignant pain: the I-WOTCH randomised controlled trial protocol. BMJ Open. 2019;9(8):e028937.
40. EuroQol G. EuroQol--a new facility for the measurement of health-related quality of life. Health Policy. 1990;16(3):199-208.
41. Fransen M, Edmonds J. Reliability and validity of the EuroQol in patients with osteoarthritis of the knee. 1999:807-13.
42. Beard DJ, Harris K, Dawson J, Doll H, Murray DW, Carr AJ, et al. Meaningful changes for the Oxford hip and knee scores after joint replacement surgery. Journal of clinical epidemiology. 2015;68:73-9.
43. Dawson J, Fitzpatrick R, Murray D, Carr A. Questionnaire on the perceptions of patients about total knee replacement. Journal of Bone and Joint Surgery (British Edition). 1998;80:63-9.
44. Dawson J, Beard DJ, McKibbin H, Harris K, Jenkinson C, Price aJ. Development of a patient-reported outcome measure of activity and participation (the OKSAPQ) to supplement the Oxford knee score. Bone and Joint Journal. 2014;96 B:332-8.
45. Stone AA, Broderick JE, Junghaenel DU, Schneider S, Schwartz JE. PROMIS fatigue, pain intensity, pain interference, pain behavior, physical function, depression, anxiety, and anger scales demonstrate ecological validity. J Clin Epidemiol. 2016;74:194-206.
46. Rolfson O, Bohm E, Franklin P, Lyman S, Denissen G, Dawson J, et al. Patient-reported outcome measures in arthroplasty registries Report of the Patient-Reported Outcome Measures Working Group of the International Society of Arthroplasty Registries Part II. Recommendations for selection, administration, and analysis. Acta Orthop. 2016;87 Suppl 1:9-23.
47. Kamper SJ, Maher CG, Mackay G. Global rating of change scales: a review of strengths and weaknesses and considerations for design. J Man Manip Ther. 2009;17(3):163-70.
48. National Clinical Guideline C. National Institute for Health and Clinical Excellence: Guidance. Osteoarthritis: Care and Management in Adults. London: National Institute for Health and Care Excellence (UK)

49. Altman DG, Bland JM. Treatment allocation by minimisation. Bmj. 2005;330(7495):843.
50. NICE. Joint replacement (primary): hip, knee and shoulder [NG157]. London, UK: NICE; 2020.
51. Hoffmann TC, Glasziou PP, Boutron I, Milne R, Perera R, Moher D, et al. Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. Bmj. 2014;348:g1687.
52. Slade SC, Dionne CE, Underwood M, Buchbinder R. Consensus on Exercise Reporting Template (CERT): Explanation and Elaboration Statement. Br J Sports Med. 2016;50(23):1428-37.
53. George AJT, Collett C, Carr AJ, Holm S, Bale C, Burton S, et al. When should placebo surgery as a control in clinical trials be carried out? The Bulletin of the Royal College of Surgeons of England. 2016;98(2):75-9.
54. Metcalfe A, Parsons H, Parsons N, Brown J, Fox J, Mannion EG, et al. Subacromial balloon spacer for irreparable rotator cuff tears of the shoulder (START: REACTS): a group-sequential, double-blind, multicentre randomised controlled trial. The Lancet. 2022;399(10339):1954-63.
55. Thompson SM, Salmon LJ, Webb JM, Pinczewski LA, Roe JP. Construct validity and test re-test reliability of the forgotten joint score. The Journal of arthroplasty. 2015;30(11):1902-5.
56. Clement ND, Scott CE, Hamilton DF, MacDonald D, Howie CR. Meaningful values in the Forgotten Joint Score after total knee arthroplasty. The Bone & Joint Journal. 2021;103(5):846-54.

57. NICE U. Guide to the methods of technology appraisal. National Institute for Health and Clinical Excellence (NICE) London, UK. 2013.
58. Curtis LA, Burns A. Unit costs of health and social care 2015: Personal Social Services Research Unit; 2015.
59. Manca A, Hawkins N, Sculpher MJ. Estimating mean QALYs in trial-based cost-effectiveness analysis: the importance of controlling for baseline utility. Health economics. 2005;14(5):487-96.
60. Sterne JA, White IR, Carlin JB, Spratt M, Royston P, Kenward MG, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. Bmj. 2009;338.
61. White IR, Horton NJ, Carpenter J, Pocock SJ. Strategy for intention to treat analysis in randomised trials with missing outcome data. Bmj. 2011;342.

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1,4
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	5
	2b	All items from the World Health Organization Trial Registration Data Set	-
Protocol version	3	Date and version identifier	5
Funding	4	Sources and types of financial, material, and other support	13
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	13
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	13
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	5

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3-4
	6b	Explanation for choice of comparators	3-4
Objectives	7	Specific objectives or hypotheses	4
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	4,7
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	9
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8-9
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10-11
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	10
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	11
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	-
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7-8
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	7

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	14	
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	10	
Methods: Assignment of interventions (for controlled trials)				
Allocation:				
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	10	
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	10	
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	10	
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	11	
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	12	
Methods: Data collection, management, and analysis				
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol		7-8
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	7-8	

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	8
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	14
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	14
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	14
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	7
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	-
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	13
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	-
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	3
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	-

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	9
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	-
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	8
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	17
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	-
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	-
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	16
	31b	Authorship eligibility guidelines and any intended use of professional writers	-
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	-
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	-
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	-

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.