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Clinical and cost-effectiveness of Knee Arthroplasty versus Joint Distraction for Osteoarthritis (KARDS): protocol for a multicentre, phase III, randomised control trial

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ABSTRACT

Introduction Knee replacement (KR) is a clinically proven procedure typically offered to patients with severe knee osteoarthritis (OA) to relieve pain and improve quality of life. However, artificial joints fail over time, requiring revision associated with higher mortality and inferior outcomes. With more young people presenting with knee OA and increasing life expectancy, there is an unmet need to postpone time to first KR. Knee joint distraction (KJD), the practice of using external fixators to open up knee joint space, is proposed as potentially effective to preserve the joint following initial studies in the Netherlands, however, has not been researched within an NHS setting. The KARDS trial will investigate whether KJD is non-inferior to KR in terms of patient-reported postoperative pain 12 months post-surgery.

Methods and analysis KARDS is a phase III, multicentre, pragmatic, open-label, individually randomised controlled non-inferiority trial comparing KJD with KR in patients with severe knee OA, employing a hybrid-expertise design, with internal pilot phase and process evaluation. 344 participants will be randomised (1:1) to KJD or KR. The primary outcome measure is the Knee Injury and Osteoarthritis Outcomes Score (KOOS) pain domain score at 12 months post-operation. Secondary outcome measures include patient-reported overall KOOS, Pain Visual Analogue Scale and Oxford Knee Scores, knee function assessments, joint space width, complications and further interventions over 24 months post-operation. Per patient cost difference between KR and KJD and cost per quality-adjusted life year (QALY) gained over 24 months will be estimated within trial, and incremental cost per QALY gained over 20 years by KJD relative to KR predicted using decision analytic modelling.

Ethics and dissemination Ethics approval was obtained from the Research Ethics Committee (REC) and Health Research Authority (HRA). Trial results will be disseminated at clinical conferences, through relevant patient groups and published in peer-reviewed journals.

Strengths and limitations of this study

- ⇒ The Knee Arthroplasty versus Joint Distraction for Osteoarthritis trial is a pragmatic trial design using standardised surgical and assessment techniques, robust reporting and safety mechanisms and appropriate sample size.
- ⇒ A hybrid-expertise-based design has been adopted to ensure feasibility of the trial while accounting for surgeon experience and potential lack of individual equipoise.
- ⇒ A surgical manual will document each trial procedure highlighting mandatory components according to recommended guidance for surgery trials. This will allow comprehensive reporting of the interventions delivered during the trial.
- ⇒ Due to the nature of the interventions, the trial personnel and participants are not blinded to treatment allocation.

Trial registration number ISRCTN14879004; recruitment opened April 2021.

BACKGROUND

Osteoarthritis (OA) is the most common musculoskeletal condition that affects joints, causing pain, joint dysfunction and significant quality of life (QoL) impact. With rising obesity rates and ageing population, the number of people presenting with knee OA is increasing.[1]

Patients with severe knee OA experiencing joint symptoms that substantially impact QoL are typically offered knee replacement (KR) to relieve pain and improve mobility. KR is clinically proven and cost-effective;[2] however,

artificial joints have a finite life span. If KR fails, revision is complex, costly and associated with higher morbidity, mortality and inferior outcomes.[3–5]

The James Lind Alliance established that defining the optimum timing of joint replacement, in order to achieve the best outcome is a significant patient concern.[6] The number of young patients (55 years or less) undergoing KR are increasing,[5] and risk of failure is disproportionately higher in the young and active. A combined endpoint analysis including revision, poor function and significant pain has shown KR success to be as low as 59% after 12 years in patients 60 years or less.[7] Increasing life expectancy and the growing number of younger patients means there is a need for treatment, which postpones the time to first KR, without compromising QoL or hampering ability to undergo KR at a later stage.[7 8] As in joint replacement in general, it is unknown whether treatment options preserving the joint are cost-effective.[9 10]

Knee joint distraction (KJD), the practice of placing an external fixator across a synovial joint and pulling the joint surfaces apart approximately 5 mm for ~6 weeks, has been proposed as a potentially effective alternative to preserve the joint. The aim is to harness intrinsic joint-repair potential, providing cartilage repair and normalisation of subchondral bone abnormalities.[11] KJD is not currently widely used in the UK, and no trials have been conducted in the NHS. Initial studies conducted in the Netherlands suggest it is a safe and potentially effective treatment.[12–14] One small trial suggested KJD to be non-inferior to total KR in function[15–17] and another predicted that it could save over 30% of revision KRs.[18] With a willingness to pay €20 000 per quality-adjusted life year (QALY), KJD was shown to be cost-effective in over 75% cases for all age groups and over 90% in the young (55 years or less).[19]

Rationale

There is strong scientific basis for KJD with excellent cartilage regeneration in experimental OA with joint offloading procedures.[20] Given the preliminary clinical data and underpinning science, KJD could be an alternative therapy to KR for younger patients, but current evidence is limited. Patient feedback highlighted the key priority for those in this age group is retaining their own knee, at expense of some residual knee pain. If KJD is shown to be safe, non-inferior to KR in terms of pain and cost-effective in the NHS, then it could be routinely offered to patients 65 years or less, delaying need for KR and potentially avoiding revision surgery. This is the aim of the Knee Arthroplasty versus joint distraction for osteoarthritis (KARDS) trial.

METHODS AND DESIGN

Objectives

The primary objective is to conduct a multicentre trial to investigate clinical effectiveness of KJD compared with KR in patients aged 65 years or less, with symptomatic knee OA severe enough to warrant KR, based on patient reported pain 12 months after surgery.

Secondary objectives are to investigate: (1) patient-reported outcomes, (2) clinical outcomes of knee function, (3) complications and need for further intervention, (4) cost-effectiveness, (5) participant experiences, intervention fidelity and barriers to wider implementation.

Trial design

This publication describes KARDS protocol V.2.0, dated 29th September 2020.

KARDS is a phase III IDEAL stage 3 assessment,[21] multicentre, pragmatic, open-label, 1:1, two-arm individually randomised controlled trial, with embedded 12-month internal pilot phase.

The internal pilot phase will incorporate a qualitative process evaluation to identify potential barriers to recruitment and any challenges experienced in maintaining intervention fidelity. As part of the process evaluation, qualitative semi-structured interviews will be undertaken with clinicians, trial staff and participants to explore experiences of trial involvement and intervention acceptability during the pilot phase and throughout the main trial. Progression at the end of the pilot phase will be based on (1) recruitment and dropout rates, (2) safety, (3) the process evaluation.

Trial setting and recruitment

Participants will be recruited from secondary care orthopaedic centres following general practitioner (GP) or specialist referral. Potentially eligible participants will be identified by the attending clinical team from orthopaedic outpatient clinics and theatre lists. Following information provision, patients will be given the opportunity to discuss the trial with their family, friends and healthcare professionals before being invited to participate.

Informed consent will be obtained by the Principal Investigator (PI) or appropriate, delegated, healthcare professional as detailed on the Authorised Personnel Log, in accordance with the principles of Good Clinical Practice and Declaration of Helsinki 1996.

All sites must be able to deliver both KR and KJD. As KJD is not a standard technique used in knee surgery, not all surgeons will have the required experience, and some surgeons may not be in individual equipoise despite there being centre equipoise. A hybrid expertise-based design, where surgeons are categorised into 'delivery units' based on experience, addresses both issues.

There are two delivery unit categories based on the interventions surgeons are authorised to perform within the trial: (1) *single delivery units* consist of surgeons authorised to deliver KJD **or** KR, where the surgeon performing the procedure will be chosen after randomisation, depending on the allocation or (2) *dual delivery units*, consisting surgeons authorised to deliver KJD **and** KR where a randomised participant may receive either operation by the same surgeon.

Table 1 Patienteligibility criteria

Inclusion criteria	Exclusion criteria
Age≥18 years and ≤65 years at time of signing the Informed Consent form	Bone density not sufficient to support pins for 6 weeks*
Symptoms (pain and/or reduced function) severe enough to warrant knee replacement*	Isolated patella-femoral OA*
Pre-operative leg alignment not requiring correction*	Complete joint space obliteration in both medial and lateral tibio-femoral compartments as seen on weight bearing AP knee radiograph
Intact collateral knee ligaments*	A known diagnosis of inflammatory arthritis
Fixed flexion deformity ≤10°	Presence of a previous joint replacement in any limb
	Surgical treatment of involved knee within the past 6 months (excluding arthroscopy)
	Previous knee joint distraction on the involved knee
	Previously participated in the KARDS trial
	Weight >120 kg
	Pregnant or lactating (confirmed by participant)
	Active cancer (currently diagnosed and under treatment)
	Unable to complete all trial procedures (eg, attend follow-up visits, complete questionnaires)
	Unable to provide informed consent (cognitive disorder such as dementia, psychiatric illness)

*In the opinion of the treating clinician.

Eligibility

Surgeon eligibility: participating surgeons must either be a consultant orthopaedic surgeon or perform the procedure under direct consultant supervision. To deliver KR within KARDS, a surgeon must have performed ≥10 KRs in the past 12 months as the primary surgeon. To deliver KJD within KARDS, they must have performed ≥10 external fixations during their career as the primary surgeon or completed a limb reconstruction fellowship.

Patient eligibility: criteria are minimised to ensure inclusivity and generalisability. Adult patients are eligible if aged ≤65 years requiring KR and meet the criteria in table 1.

Interventions

A surgical manual will document each trial procedure highlighting mandatory components according to recommended guidance.[22]

Intervention (KJD)

A definitive external fixator construct will be used, which allows for controlled linear distraction across the knee joint of 5 mm. The exact nature of the construct will depend on equipment availability at site and surgeon preference. Devices will be approved for trial use by the Trial Management Group.

During surgery, the external fixation frame will be assembled according to frame construct procedures detailed in the surgical manual, with focus on meticulous pin insertion to minimise complication risk. Pins will be placed under fluoroscopic control. Once assembly completes, ≥2 mm and ≤5 mm axial distraction will be applied across the knee joint. A further 1 mm distraction may be applied per day until 5 mm distraction at the joint is confirmed radiographically, or up to 7 days.

External fixators will be removed under general or regional anaesthesia after 6 weeks. Local protocol for pin-site care will be followed and will be documented. Gentle manipulation under anaesthesia to achieve ≥90° of motion will be attempted at the time of fixator removal.

Control (KR)

KR surgery will be performed in line with local practice and the surgical manual and will vary depending on implant type and surgeon preference. Surgeons performing the procedure are expected to comply with specific surgical steps for the implant being used as detailed in the manufacturer instructions for use document.

Concomitant care and interventions

Pre-operative preparation and post-operative care will be provided to all trial participants in line with the site's usual protocol for KRs. Decisions about concomitant medications/treatments for symptomatic knee osteoarthritis will be according to local medical plan and clinical management. Details of analgesia and other medication prescribed will be collected throughout trial. Participants may require further intervention for symptomatic knee OA as per routine practice. Further clinical intervention is permitted for all participants and recorded for the trial.

Patient and public involvement

KARDS patient and public involvement (PPI) group provided feedback on choice of primary outcome,

minimally important difference used in sample size calculations and the decision to not blind participants. PPI representatives on the Trial Management Group provided feedback on the schedule of events for participants.

Randomisation and blinding

Participants will be randomised into the trial by an authorised member of site staff, on a 1:1 basis between KJD and KR, based on a minimisation algorithm with random component balanced for delivery unit and OA severity (Kellgren-Lawrence grades 2–3 versus grade 4).[23] Randomisation will be performed centrally using Leeds Clinical Trials Research Unit (CTRU) automated secure 24-hour randomisation web or telephone service, occurring on the same day as baseline visit, within 6 weeks of the planned surgery date. Clinical assessments and baseline questionnaires will be completed before randomisation with trial specific assessments performed afterwards. Treatment allocation will not be blinded to participants, medical staff or clinical trial staff.

Data collection

Clinical data will be collected at baseline, day of surgery, prior to discharge, week 6 (KJD only), and months 3, 12 and 24 post-surgery. Participant completed data will be collected at baseline, day of surgery and months 3, 6, 12 and 24 post-surgery. Full assessment schedule based on the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidance is[24] provided in online supplemental material 1.

Participating sites will maintain a file of essential trial documentation including copies of all completed Case Report Forms (CRFs). Sites will post paper CRFs and electronically transfer trial X-rays to Leeds CTRU. Trial data will be entered onto an electronic database, except post-surgery questionnaires completed using electronic remote data capture by participants or via postal questionnaire.

Data will be monitored for quality and completeness by CTRU. Missing data will be requested from sites until received, confirmed as unavailable or trial analysis begins. The sponsor reserves the right to conduct periodic source data verification to monitor trial integrity.

Participant qualitative interviews will be conducted by telephone, and staff interviews conducted in person or telephone/video conference. Interviews will be audio recorded on an encrypted recorder, anonymised and transcribed verbatim for analysis.

All information collected during the trial will be kept strictly confidential. Information will be held securely on paper and electronically at Leeds CTRU, with process evaluation data held securely on Warwick Clinical Trials Unit (CTU) server. Both will comply with all aspects of the Data Protection Act 2018. If a participant withdraws consent from further trial treatment and/or further data collection, data to the point of withdrawal will remain on file and included in the analysis.

Outcome measures

Primary outcome measure

The primary outcome measure is Knee Injury and Osteoarthritis Outcomes Score (KOOS) pain score 12 months post-surgery. Pain was indicated by the PPI group as being the most important outcome to them. KOOS is a patient-administered questionnaire, validated for use in patients with knee OA or knee injury,[25] recorded on a Likert Scale 0–4, transformed to 0 (worst) to 100 (best) scale.

Secondary outcome measures

1. *Patient report outcome measures (PROMs) and QoL within 24 months post-surgery*
   a. KOOS (overall and at component level).
   b. Pain Visual Analogue Scale (VAS).[26 27]
   c. Oxford Knee Score (OKS).[28–30]
2. *Objective assessment of knee function*
   a. Active range of movement.
   b. Timed-up-and-go test.[31 32]
3. *Incidence of complications, including infection*
   a. Intra-operative complications.
   b. Post-operative complications.[33]
4. *Further interventions within 24 months postsurgery*
   a. Further surgical interventions including conversion to KR or revision surgery.
5. *KJD's potential as cartilage regenerative therapy*
   a. Joint space width (assessed using standardised fixed flexion PA at 20° X-rays[34]).
6. *Estimate of short-term and long-term cost-effectiveness*
   a. EuroQol 5 Dimensions (EQ-5D)-3L questionnaire at 24 months.
   b. Health Resource Utilisation and Private Costs questionnaire at 24 months.
   c. Incremental costs per QALY gained at 20 years.
7. Implementation processes and intervention fidelity
   a. Quantitative (surgical CRF and central review of post-operative X-rays).
   b. Qualitative evaluation with surgical and clinical staff.
8. Qualitative evaluation of participant experiences.

Statistical considerations and analyses

Sample size

Power calculations are based on a non-inferiority hypothesis for the primary outcome measure, KOOS pain score. 344 participants (172 per arm) will have 90% power to demonstrate non-inferiority based on an 8 point non-inferiority margin, assuming an SD of 21 points,[2 35–37] one-sided 2.5% significance level and 15% dropout rate. The non-inferiority margin was agreed by clinical and patient co-applicants based on being 33% less than the 12 point minimally important difference observed in previous trials,[18 38–40] clinical co-applicant experience and PPI focus group feedback. No adjustment has been made to accommodate surgeon learning curve since external fixation is a common procedure orthopaedic surgeons frequently do for trauma, and minimum expertise is required for surgeon eligibility.

Analysis methods

Full statistical analysis plan predefining all analyses and patient populations will be in place prior to any comparative analyses according to guidelines.[41] KARDS will be reported according to the Consolidated Standards of Reporting Trials extension for Non-Inferiority and Equivalence Randomised Trials.[42] The intention-to-treat (ITT) population will include all randomised participants, and the per-protocol (PP) population will include all participants who received their randomised intervention as intended. Although there is no 'gold standard' for non-inferiority trials, outcomes will be analysed primarily for the PP population.[43] A sensitivity analysis will be conducted for the ITT population.

The primary analysis will report adjusted estimates of treatment effect from multivariable regression of KOOS pain score at 12 months. Statistical significance of KJD non-inferiority relative to KR will be based on a 2-sided likelihood-based test with type 1 error of 2.5% in both tails, adjusted by baseline score and OA severity as fixed effects, and delivery unit as a random effect.[44] If the 95% confidence interval (CI) for absolute difference in means between KJD and KR lies entirely below or includes the non-inferiority boundary, then there would be insufficient evidence to reject the null hypothesis that KJD inferior to KR. Conversely, if the 95% CI lies entirely above the non-inferiority boundary, there would be evidence to reject the null hypothesis and conclude KJD non-inferior to KR. If non-inferiority demonstrated and KJD appears superior to KR, based on estimated effect and associated CI, statistical significance for superiority will be calculated based on an ITT analysis. Secondary analysis of the primary outcome measure will use multilevel modelling to account for longitudinal data collected over 24 months. Sensitivity analyses will be considered to investigate any impact of surgeon experience on treatment effect estimates.[45]

Reasons for missing data will be examined and primary method to account for missing data will be chosen based on the most reasonable missing data mechanism assumption, with sensitivity analyses to assess robustness of results to different missing data mechanism assumptions.

Other PROM responses will be transformed into dimension scores, according to scoring manuals, and presented graphically and longitudinally. Standardised area under the curve (AUC) statistics will be compared across treatment groups as an analysis conditional on patient time in the trial. Functional assessments will be reported descriptively, along with joint space width for the KJD group.

Complications will be reported as unique events and unique patients experiencing events. Joint survival will be measured from randomisation to time of further intervention and analysed using the Kaplan-Meier method.

Process evaluation interview data will be analysed using thematic content analysis to identify patterns or themes,[46] using coding of audio-transcript recordings, adopting the framework method described by Ritchie and Spencer and Pope and Mays.[47 48] Normalisation Process Theory will be used as a theoretical framework to explore and explain extent of intervention implementation,[49–51] using the software package NVivo V.12 to manage data and facilitate this process. Interview data and full record of issues raised will be discussed in detail with the Trial Management Group and summarised for oversight committees. Good practice will be shared with other recruiting sites.

Cost-effectiveness analysis will be conducted from NHS and Personal Social Services perspectives and society over a 24-month time horizon. The analysis will estimate surgical intervention costs and primary and secondary healthcare services costs including complications, follow-up, medications and repeat medical procedures and out of pocket and productivity costs to patients and their families. Outcomes will be evaluated using QALYs estimated by the AUC approach. Unit costs will be obtained from list prices for devices and materials involved in the interventions, medications list prices, NHS health professional staff salary scales, primary care and community services opportunity costs,[52] outpatient, inpatient admissions and Accident and Emergency visits NHS Reference Costs and median UK gross hourly earnings.[53] Generalised linear models will be used to adjust for unbalanced baseline covariates in costs[54 55] and adjusting for baseline EQ-5D-3L score in analysing QALYs.[56] Missing data will be imputed using established methods.[57] Results will be presented in terms of incremental cost per QALY gained and cost per unit gain in 12-month KOOS. Sampling uncertainty will be analysed using the bootstrap method[58] and joint uncertainty in costs and QALYs will be analysed using cost-effectiveness acceptability curves.[59]

A decision analytic model will be built to evaluate lifetime cost-effectiveness over 20 years by adapting and updating a published Markov model of delayed joint replacement using National Joint Registry, clinical study and UK life table data.[9 10] The model will account for trade-offs of delaying KR in terms of reducing the risk of the patient requiring revision surgery near end of life and increased complication risk with primary operation at older age.[9] Sampling uncertainty in model parameter values will be described using probabilistic sensitivity analysis, while key parameters affecting the likelihood of KJD meeting the NICE £20 000 threshold for cost-effectiveness[60] will be identified using Tornado plots.

Monitoring

An independent Trial Steering Committee (TSC), comprising a statistician, two orthopaedic consultant surgeons and one patient representative, will have overall responsibility for trial oversight, monitoring trial progress, protocol adherence and participant safety. An independent Data Monitoring and Ethics Committee (DMEC) comprising a statistician and two orthopaedic consultant surgeons will review interim safety data by randomised group, reviewing the underlying statistical design assumptions to ensure the trial remains adequately powered. TSC and DMEC meetings will be conducted annually

as a minimum according to agreed TSC and DMEC Charters.[61]

No formal guidelines for stopping the trial early are in place since no formal planned interim analysis of the primary outcome is planned.

Information on complications will be collected from randomisation to end of trial defined as the last visit date of the last patient. Serious complications will be subjected to expedited reporting where sites will inform CTRU within 24 hours of becoming aware of it. Suspected or confirmed pregnancies and all deaths from randomisation until the end of trial will be reported to CTRU.

ETHICS AND DISSEMINATION

KARDS is funded by NIHR HTA (reference: 17/122/06) and sponsored by the University of Leeds, approved by the Research Ethics Committee (REC) (reference: 19/YH/0368) and Health Research Authority (HRA). All amendments will be submitted for approval and communicated to sites in accordance with HRA guidelines.

Trial results will be disseminated at relevant clinical conferences and societies, published in peer-reviewed journals and disseminated through relevant patient groups. Authorship will be according to International Committee of Medical Journal Editors (ICMJE) guidelines.

DISCUSSION

KARDS is a pragmatic, multicentre prospective randomised controlled trial conducted in an NHS setting, the aim is to determine if KJD is non-inferior to KR in terms of pain and cost-effective in the NHS, then it could be routinely offered to patients aged 65 years or less. In addition, it will report on radiological outcomes and patient acceptability. It will be a definitive IDEAL stage 3 (Assessment) trial[21] with potential to lead to a paradigm shift if it demonstrates non-inferiority of KJD compared with KR.

Joint distraction outcomes at various anatomical locations have been reported in several case series. Though small numbers of patients have been involved, results are encouraging in at least providing temporary symptom relief. At the ankle, improvements in reported symptoms were seen in 73%–91% of patients at mean follow-up time of 1–12 years.[62] Joint distraction has been demonstrated to give good clinical outcomes in first carpometacarpal joint osteoarthritis, albeit in a very limited number of patients. Patients were followed for 1 year with improved functional scores compared with baseline.[63] The KJD literature is difficult to assess due to heterogeneity of devices and methods used. A recent review included one cohort study and two small trials all of which came from the same research group, including a total of 62 patients.[64] These studies all utilised a spring-loaded static distractor. Western Ontario and McMaster Universities Osteoarthritis Index score improvements were significantly greater 1 year post KJD than conservatively managed osteoarthritis,[17] and not inferior to total KR[19] or high tibial osteotomy (HTO).[11]

Two studies[11 19] reported KOOS, Intermittent and Constant Osteoarthritis Pain score, EQ-5D and Short Form (SF)−36 with significant improvements at 1 year seen in all scores except for the SF-36 mental component score, with no significant difference in these improvements compared with KR or HTO. Pain score assessed on pain VAS was reported in both studies and showed improvements at 1 year with no significant difference between KJD and HTO or KR. Radiographic assessment of joint structure has been undertaken in various studies, with imaging at the time of distraction or follow-up. The group above used MRI to assess structural recovery. Mean cartilage thickness was shown to increase on both the tibial and femoral sides and percentage of joint surface appearing as denuded subchondral bone decreased.[64] Radiographic minimum joint space width was shown to increase by 0.8 mm at 12 months compared with baseline.[11 17 19] Similar to another study where the mean joint space width, measured using standardised digital techniques, increased from 2.7 mm to 3.6 mm 12 months post-fixator removal.[65]

The most frequently reported KJD complication is pin site infection. Rates approaching 70% have been reported, with 20% of affected patients requiring intravenous therapy.[64] In the series of 62 patients described above, two patients required surgical intervention for pin-site infection during distraction, with a further case of osteomyelitis requiring surgery following fixator removal.[11 17 19] These infection rates are at odds with those reported in patients treated by definitive external fixation for other reasons. Pin-site infection rates of 40% are found fairly consistently, even where fixators are in place for much longer, the reasons for this are unclear.[66] While transient pin-site infection seldom has long-term implications, it is unpleasant for patients and may impair rehabilitation. Deep infections may be more worrisome, especially considering expected osteoarthritis progression following distraction potentially requiring eventual arthroplasty. Wherever possible, external fixator pins will be sited outside the implantation zone of a KR. Total KR following significant osteomyelitis is significantly more complex and has further infection risk even when infection considered eradicated.[67] Current KJD literature does not provide sufficient evidence to estimate serious infection rates following conversion to KR. In one ankle distraction study with over 5-year follow-up, there was no infection seen in five patients who had conversion to arthroplasty.[68] Loss of knee range of movement immediately following distraction therapy has been observed to return after 1 year, with a small number of patients undergoing joint manipulation under anaesthetic to achieve this.[13 19]

Trial strengths include its pragmatic nature, standardised surgical and assessment techniques, robust reporting and safety mechanisms and appropriate sample size. The window of 6 weeks between baseline measures

and planned surgery date aligns with clinical pathways and ensures recruitment feasibility. KARDS has a pragmatic hybrid expertise-based design, where surgeons are categorised into 'delivery units' based on their experience, a successful approach in similar knee OA surgical trials.[69] Furthermore, clinicians are free to choose KR implant type and KJD external fixator. This choice brings a limitation in not being able to determine potential individual mechanisms of action limiting individual indications and/or contraindications. Those implants and fixators approved in the trial protocol are based on consensus among experts and published literature. Subgroup analysis will not be adequately powered to determine if a particular fixator type is superior. A further limitation is the lack of blinding, but this is unavoidable. It would be impractical to blind medical staff prior to surgery at many sites as they need to plan for the specific surgery. PPI feedback was that being blinded until just before or after surgery would be unacceptable if the medical team knew the allocation. The primary outcome measure is patient reported and, therefore, it is not possible to have a blinded primary outcome assessment.

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Competing interests HS—consultant to Orthofix and received research grant from Orthofix. Received payment for teaching responsibilities from Orthofix and Smith & Nephew. HP—received grant funding from KTP, Pacira Pharmaceuticals, Zimmer Biomet Healthcare, B Braun & Welcome Trust. Received consulting fees from Medacta International, Smith and Nephew, Depuy Synthes, JRI Orthopaedics, Janssen, Meril Life, Zimmer Biomet & Paradigm Pharmaceuticals. Received payment from Invibio for presentations, from Kennedy's Law for expert testimony & from Pacira Pharmaceuticals for study conduct. Received payments from Medacta International, Depuy Synthes & Zimmer Biomet for attending meetings/travel. HSi—received grant funding from EPSRC Ultrasonic Surgery & EPSRC 2050 EnLightenus. Submitted patent with Joint Assist patient application. AM—received grant funding from Stryker for the RACER-Hip trial.

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	Screening and Consent	**Randomisation & Baseline**		**Surgery (Day 0)**	**Follow-up time point**						**Unscheduled**
					Clinic visits			**Postal questionnaire packs**	**Clinic visits**		
	Prior to registration	Before randomisation and within 6 weeks prior to surgery	After randomisation and within 6 weeks prior to surgery		Post-operative (Up to Day 7)	Fixator Removal (Week 6)	Follow up (Month 3)	Follow up (Month 6)	Follow up (Month 12)	Follow up (Month 24)	
	All	All	All	All	All	KJD arm only	All	All	All	All	All
Informed Consent	X										
Screening Data	X										
Eligibility	X										
Patient Details	X										
Patient Demographics		X									
Medical History		X									
OA Severity (Kellgren-Lawrence grade based on standard AP & lateral x-rays)		X									
Physical examination of knee		X									
TUG (Timed up and go test)		X					X		X	X	
ROM (Range of movement) using goniometer		X					X		X	X	
Rosenberg View X-ray			X				X^		X^	X^	
Surgery (KR or KJD)				X							
Surgical details				X		X^					
Distraction of external fixator (KJD only)				X^	X^						
Removal of external fixator (KJD only)						X^					
Intra-operative Complications				X		X^					
Additional knee related and/or other limb surgery				X	X	X^	X	X	X	X	X
Concomitant Medications				X	X	X^	X	X	X	X	X
Discharge Details					X	X^					

AP/Lateral View X-rays					X	X^					
Post-operative Complications					X	X^	X	X	X	X	X
Patient Reported Outcomes											
KOOS		X		X*			X	X	X	X	
OKS		X					X	X	X	X	
EQ5D-3L		X					X	X	X	X	
Pain VAS		X					X	X	X	X	
Health Resource Use		X					X	X	X	X	
Serious complications											X
Participant withdrawal											X
Re-operation											X
Pregnancy											X
Death											X

*Up to 1 day before surgery
^KJD arm only